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But... Was There Ever a Clark Classification of Melanomas?

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Abstract
For the past 40 years, the Clark classification of cutaneous melanoma has been accepted and used by the vast majority of dermatologists and pathologists throughout the world. However, after careful rereading of the most relevant articles by Clark and his collaborators, we can affirm that the classification was only ever of passing validity. After distinguishing between nodular melanoma, superficial spreading melanoma (SSM), and lentigo maligna melanoma (LMM) in 1968, the inclusion of acral-lentiginous melanoma (ALM) in 1979 as a new subtype was the first serious setback for the classification; in contrast to ALM, late-onset lentiginous melanomas, such as LMM, were situated on areas of skin with less exposure to sunlight.
Later, the same authors found that, contrary to their initial belief, the prognosis of LMM was the same as that of other subtypes with the same Breslow thickness. Finally, a number of observations by the same authors made ever clearer the increasing difficulty for distinguishing microscopically between LMM, SSM, and ALM, except by taking their localization into consideration. This means that, today, the possible morphological differences between one case of cutaneous melanoma and another are of no proven prognostic implication. In addition, the morphological differences that can be found are much more closely related to the different localization than to the tumor itself.
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PALABRAS CLAVE
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Breslow

Pero… ¿hubo alguna vez una clasificación de Clark de los melanomas?

Resumen
Desde hace 40 años, la inmensa mayoría de los dermatólogos y los patólogos de todo el mundo ha aceptado y ha empleado la clasificación de Clark de los melanomas cutáneos. Sin embargo, tras una cuidadosa relectura de los artículos fundamentales de Clark y sus colaboradores, hemos podido comprobar que tal clasificación ha sido en realidad muy efímera.
Tras distinguir en 1968 entre melanoma nodular, melanoma de extensión superficial (MES) y melanoma del lentigo maligno (MLM), la inclusión en 1979 del melanoma lentiginoso acro (MLA) como un nuevo subtipo de melanoma fue la primera avería seria de la clasificación, ya que un melanoma lentiginoso y de aparición tardía (como el MLM) se localizaba, a diferencia de éste, en las zonas menos fotoexpuestas de la piel. Posteriormente, los mismos autores comprobaron que, contrariamente a su idea inicial, el pronóstico del MLM era el mismo que el de los demás subtipos a igualdad de espesor, según Breslow. Finalmente, diversas observaciones de los mismos autores fueron poniendo de manifiesto su creciente dificultad para distinguir al microscopio entre MLM, MES y MLA, salvo que tuviesen en cuenta la localización.
Es decir, que hoy por hoy las posibles diferencias morfológicas entre uno y otro caso de melanoma cutáneo no conllevan demostradas diferencias pronósticas, y las diferencias morfológicas que puedan encontrarse se deben más a la diferente localización que a la propia neoplasia.
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Over the past 40 years, nearly all the dermatologists and pathologists in the world have categorized, or attempted to categorize, every case of cutaneous melanoma they encountered according to Clark's classification. However, a careful rereading of the most relevant papers on the subject by Clark and his colleagues has given rise in our minds to a reasonable doubt not only concerning the prognostic usefulness of this classification and the criteria it is based on, but even concerning the very existence of this supposed classification system. We have in fact come to pose the question of whether there ever really was a Clark classification of melanomas.

The first international consensus on the nomenclature and classification of cutaneous melanoma and on the procedures that physicians should follow in patients with a lesion of this type was adopted at the International Cancer Conference held in Sydney, Australia, in March 1972. The results of that meeting were published in 1973[1] and the

Table 1 List of Terminology Recommended by the International Cancer Conference (Sydney, 1973) for the Denomination of the Different Types of Melanoma[a]

Recommended Terminology	Synonyms in Common Use
Hutchinson's melanotic freckle	Hutchinson's freckle Senile freckle Lentigo maligna Circumscribed precancerous melanosis of Dubreuilh Dubreuilh's melanosis circumscripta precancerosa
Superficial spreading melanoma, noninvasive	Pagetoid melanoma Premalignant melanosis Circumscribed precancerous melanosis of Dubreuilh Dubreuilh's melanosis circumscripta precancerosa) In situ melanoma
Melanoma, invasive, with adjacent intraepidermal component of Hutchinson's melanotic freckle type	Lentigo maligna melanoma
Melanoma, invasive, with adjacent intraepidermal component of superficial spreading type	Superficial spreading melanoma Pagetoid melanoma Melanoma with an in situ component
Melanoma, invasive, without adjacent intraepidermal component	Nodular melanoma Melanoma d'emblée

[a]Adapted from McGovern et al.[1]

agreed nomenclature is shown in Table 1. The terminology recommended for the classification of melanomas and the other recommendations, including the level of invasion, were largely based on 4 papers published in the years leading up to the meeting,[2-5] 3 of which were authored by Clark's group.[2-4] The first of these papers was a chapter in a book published in 1967.[2] This was followed in 1969 by 2 articles (1 in March signed by Clark, From, Bernardino, and Mihm[3] and another in April signed by Clark and Mihm[4]). The first of these articles reported on 209 cases of which 114 were classified as superficial spreading melanoma (SSM), 66 as nodular melanoma (NM), and 29 as lentigo maligna melanoma (LMM). The authors considered NM to be melanoma in which they observed—after examination of many histologic sections—that intraepidermal growth, when present, did not extend more than 3 rete ridges outside the intradermal component of the tumor in any of the sections studied. In appearance NM was a nodule, that is, a clearly elevated plaque or an exophytic and often ulcerated lesion without any flat component around the central mass. This presentation was found in 30% of the patients in that case series. The other 70% of cases all presented a more or less flat component of greater or lesser extension. The clinical characteristics (shape, surface, and color) of this component were then used to divide these nonnodular cases into 2 groups, defined as SSM and LMM. However, despite establishing a series of criteria with respect to these macroscopic characteristics, the authors also stated that:

> "Histologic sections representing the various gross patterns of the primary lesion are necessary for accurate diagnosis and classification of malignant melanoma. About 70% of melanomas (SSM and LMM) have a significant portion of the primary lesion present either intraepidermally or just below the basement membrane. It is the evaluation of these superficial cells that determines the classification of melanoma [...]."[3]

And what are the characteristics of this superficial portion of the melanoma whose scant presence or total absence would classify a case of melanoma as NM and

Table 2 Characteristics of the Intraepidermal Component of Superficial Spreading Melanoma and Lentigo Maligna Melanoma According to Clark et al[a]

SSM	LMM
1. Pagetoid growth[b] • Individual cells • Nests • Masses	1. Pagetoid growth is very uncommon • There may be nests
2. NA	2. Gradual increase in the number of basal melanocytes until these replace the whole basal layer
3. "Epithelioid" melanocytes (abundant cytoplasm with dusty melanin)	3. Some cells are normal, others have large nuclei, and occasionally some are multinucleated
4. While clearly abnormal, the melanocytes are nonetheless similar one to another[c]	4. Cell pleomorphism[c]

Abbreviations: LMM, lentigo maligna melanoma; NA, not applicable; SSM, superficial spreading melanoma.
[a]Data derived from Clark et al.[3]
[b]Pagetoid growth: relatively large single melanoma cells distributed throughout all levels of the epidermis including the stratum corneum; generally associated with clearly defined nests of such cells. Nests may merge and even replace almost the whole keratinocyte population (masses).
[c]Cytology. Although the tumor cells of SSM are clearly abnormal, "contiguous cells tend to be similar, which is in contrast to lentigo maligna melanoma where there is more variation in cell structure." In LMM, "the melanocytes may vary markedly in form; some appear essentially normal; others have large nuclei or may be multinucleated."

Table 3 Levels of Invasion and Outcomes[a]

	No. of	% (Years of Follow-up)[b]	
	Cases	Deaths[c]	Survivors[d,1].
Level I (melanoma in situ)	0		
Level II (partial invasion of the papillary dermis)	36	08.3 (1.5)	72.2 (6.8)
Level III (total invasion of the papillary dermis)	71	35.2 (2.8)	46.5 (6.8)
Level IV (invasion of the reticular dermis)	76	46.1 (2.2)	31.6 (5.2)
Level V (invasion of the hypodermis)	25	52.1 (1.8)	12.0 (3.5)

[a]Data derived from Clark et al.[3] In 208 of the 209 patients it was possible to determine the level of invasion according to the criteria shown in the table.
[b]The percentages of patients who died and survived on each level do not add up to 100. The missing cases are patients who died from other causes or were lost to follow-up.
[c]Deaths from melanoma.
[d]Survivors apparently free from neoplastic disease.

whose presence allows us to distinguish between SSM and LMM? Table 2 summarizes the characteristics attributed by the authors to this intraepidermal component in SSM and LMM and includes their definitions of some terms we believe to be essential to a good understanding of their hypothesis. As well as classifying their cases by histology, they also classified the lesions according to the level of invasion and ascertained that the prognosis deteriorated with increasing depth of invasion (Table 3). Table 4 summarizes the histologic classification of the 209 cases together with the patients' ages and the outcome in each case. Table 5 summarizes the data on the sites of the tumors. On the basis of this study, the authors concluded:

> "The majority of human malignant melanomas (superficial spreading and lentigo maligna melanoma) are characterized by a relatively long period of centrifugally spreading, superficial growth (intraepidermal or just below the basement membrane) [...]"[3]
> "Lentigo maligna melanoma is a biologic entity, but are we justified in dividing the remaining melanomas into two distinct groups? [...] This view then regards nodular melanoma as a quite malignant neoplasm from the outset, but it is probably not a different biologic entity when compared with superficial spreading melanoma."[3]

They summarized their classification of melanoma into 3 distinct forms as follows:

> "First, we also distinguish lentigo maligna melanoma as a slowly growing, relatively benign neoplasm usually on the exposed surfaces of the elderly."[3]
> "Secondly, we feel that another form of melanoma, superficial spreading melanoma, also shows a relatively long period (6 months to 5 years) of superficial growth and then develops tumor nodules and deep invasion."[3]
> "Third, those tumors showing a nodular form and a tendency to deep invasion from the outset were termed nodular melanoma."[3]

The second article from 1969 is a monograph on 1 of the 3 types of melanoma described in the earlier article: LMM and its initial phase, lentigo maligna.[4] The authors start by saying:

> "This paper will describe lentigo-maligna (L-M) melanoma (Hutchinson's melanotic freckle or circumscribed precancerous melanosis of Dubreuilh). This kind of malignant melanoma begins as a small, irregular, freckle-like lesion and then evolves over many years in a distinctive way to become an invasive malignant melanoma distinguishable from the other forms of melanoma. The early, noninvasive stages of the process similar to a freckle will be referred to as lentigo maligna and the later invasive stages as L-M melanoma; this malignant melanoma occurs almost exclusively on exposed surfaces of the body and has a better prognosis than other forms of melanoma."[4]
> "In the following descriptions lentigo maligna and L-M melanoma are at times considered separately, but in spite of this division for descriptive purposes, we regard these two lesions as representing the early and late stages of a single process. The sole criterion separating lentigo maligna from L-M melanoma is the presence of invasion in the latter."[4]

The study was based on 13 cases of lentigo maligna and 35 of LMM. Table 6, which is based on the information reported

Table 4 Histologic Classification of the 209 Cases of Melanoma Studied by Clark et al[3] with Age and Outcome for Each Type of Melanoma[a]

	No (%)	Age, y	%	
		Range (mean)	Survivors[b]	Deaths[c]
SSM	114 (54.5)	12-87 (52.9)	31.5	46.5
NM	66 (31.6)	16-84 (51.8)	56.1	27.3
LMM	29 (13.9)	45-96 (70.0)	10.3	55.2

Abbreviations: LMM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma.
[a]Data derived from Clark et al.[3] The percentages of deaths and surviving patients for each type of melanoma do not add up to 100. The missing cases are patients who died from other causes or were lost to follow-up. Mean follow-up was 6 to 6.5 years for patients with SSM and NM, and 4.75 years for patients with LMM.
[b]Survivors apparently free of neoplastic disease.
[c]Deaths from melanoma.

Table 5 Distribution of Melanoma in the Cases Studied by Clark et al[a]

	SSM	NM	LMM	Total
Scalp	3	1	2	6
Head and neck	18	8	25	51
Chest	7	3	-	10
Back (above waist)	17	6	-	23
Upper arm	6	4	-	10
Forearm and dorsum hand	7	7	2	16
Hand (palm)	5	1	-	6
Hand (subungual)	1	1	-	2
Abdomen	4	2	-	6
Back (below waist)	2	5	-	7
Genitals	2	2	-	4
Thigh	3	2	-	5
Lower leg	22	8	2	32
Dorsum foot	4	1	-	5
Sole of foot	13	12	-	25
Foot (subungual)	1	1	-	2
Unknown	4	-	-	4
Total[b]	119	64	31	214

Abbreviations: LMM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma.
[a]Data derived from Clark et al.[3]
[b]The total numbers do not coincide with those of earlier tables (there are 5 more melanoma cases). This table is based on a histogram in which the bars are not accompanied by figures and the height of the bar on the scale is often difficult to determine. This table and Tables 2-4 were compiled, sometimes with difficulty, using the data reported in the paper by Clark et al.[3]

Table 6 Clinical Features of the 13 Cases of Lentigo Maligna and 35 Cases of Lentigo Maligna Melanoma (LMM) Studied by Clark and Mihn[a]

	Lentigo Maligna	LMM
Number of cases	13 lesions/13 patients	37 lesions/35 patients
Mean age on diagnosis	65	70 (45–96)
Mean age at onset	47	60.6
Interval elapsed before lentigo maligna became LMM	-	4 months–50 years
Mean size, cm	2.7 (0.3 × 0.5–3.3 × 3.3)	8.4 (0.2 × 0.2–7.5 × 6)
Site		
Face and neck	11	32
Back	1	1
Forearm	1	-
Dorsum of the hand	-	2
Pretibial	-	2
Survival		
Deaths caused by LMM	-	3[b]
Survivors with lymph node metastasis	-	3
Healthy survivors	-	18
Deaths attributable to other causes	-	9
Lost to follow-up	-	5

Abbreviations: LMM, lentigo maligna melanoma.
[a]Data derived from Clark and Mihn.[4]
[b]At 8 years and 2 months, at 1 year and 10 months, and at 1 year and 9 months after histologic diagnosis.

Table 7 Histologic Differences Between the Intraepidermal Components of Superficial Spreading Melanoma and Lentigo Maligna Melanoma According to Clark and Mihm[a]

	SSM	LMM
Pagetoid distribution	Common	Rare
Nests	Found in almost all sections	Less common
Melanocytes (atypia)	Although totally abnormal, the cells are similar one to another (all equally bad).	Marked pleomorphism with cells ranging from normal to totally atypical and multinucleated
Dominant cytology	Epithelioid	Spindle-shaped
Cytology	Large cells with abundant cytoplasm and a large nucleus	Large cells with scant cytoplasm and a large nucleus

Abbreviations: LMM, lentigo maligna melanoma; SSM, superficial spreading melanoma.
[a]Data derived from Clark and Mihm.[4]

in the article, summarizes the clinical data for these cases. The authors undertook a very meticulous histologic study of each of the clinical areas of the lesion as identified by differences in tonality (cinnamon, brown, reticulated black, flat black, etc). They then list the clinical and histologic differences between LMM and SSM. Table 7 summarizes the histologic differences, which are the most important type since the authors asserted that numerous sections of these intraepidermal portions are necessary to differentiate between the 2 processes. They conclude by saying:

> "Lentigo maligna and lentigo-maligna melanoma are names applied to early and late stages of the same neoplastic system affecting melanocytes; lentigo maligna applies to the noninvasive stage and lentigo-maligna melanoma to the invasive neoplasm."[4]

In 1977, on the basis of a study of 33 plantar melanomas from the records of a hospital in New Orleans, Arrington et al[6] concluded that:

> "[...] there are variants of cutaneous melanoma that are not adequately defined by the preceding parameters and have not been included in current classifications. In particular, melanomas of soles are distinctive."

Twenty-seven of the 33 cases had a lentiginous radial component and the other 6 were considered unclassifiable. Table 8 summarizes the clinical characteristics and outcomes of these 27 cases.

The authors of that study remarked on the marked histologic similarity between these plantar melanomas and lentigo maligna and on the fact that several authors had reported on cases of lentigo maligna affecting the mucosal membranes and subungual region. As a result, they concluded that there was "...a nonactinic lentiginous variant" of melanoma that "occurs on the palms and soles, the subungual areas, the muco-cutaneous junction of the oral and nasal cavities and the anus."[6] They compiled a table to compare the histologic features of their cases of plantar lentiginous melanoma with those of the other 2

types of melanoma with a radial component that had been described by Clark's group (Table 9).

In 1979, Clark, Goldman and Mastrangelo edited a book entitled *Human Malignant Melanoma*[7] with chapters on all aspects of ocular and cutaneous melanoma. In chapter 4,[8] Elder, Ainsworth, and Clark reviewed the histopathology of SSM, NM, and LMM and, in contrast to their earlier articles, now asserted that:

> "Difficulty may be encountered from time to time in histologic distinction among the various forms of melanoma categorized above, but if clinical as well as histologic parameters are assessed, differentiations is not usually a problem"[8]

In chapter 5 of the same book, Clark, Bernadino, Reed, and Kopf[9] reviewed the clinical and histologic characteristics of what they call acral lentiginous melanoma (ALM), which included, as Arrington et al[6] had indicated, melanomas affecting the palms, soles, nail bed, and mucous membranes, since:

> "Malignant melanomas of the superficial spreading and nodular varieties occur uncommonly in the volar and subungual sites."[9]

Thirty-seven (5.6%) of the 636 cutaneous melanomas studied by the Temple University Group occurred in volar (70%) and subungual (30%) sites. At the end of the chapter the authors summarized the histologic features of the radial growth phases of ALM, SSM, and LMM in a table (Table 10).

Having reached this juncture—the point by which Clark and his colleagues had recognized the 4 types of cutaneous melanoma that make up their famous classification—we will once again summarize the criteria they used to distinguish each variant: when little or no intraepidermal growth is present, the lesion is classified as NM; and when such growth extends beyond the width of 3 rete ridges, the histologic and cytologic features of the intraepidermal component can be used to classify the nonnodular melanoma as SSM, LMM, or ALM.[2-4,8,9]

In 1969, Clark et al[3] and Clark and Mihm[4] explained the characteristics that allowed them to differentiate between SSM and LMM; these are summarized in Tables 2 and 7. Arrington and colleagues[6] (one of whom was Reed) later identified a new variant which, in their opinion, was not adequately covered by the established criteria. This new variant, which they called plantar lentiginous melanoma, was found only on the palms and soles, the subungual areas, and the muco-cutaneous junctions.

In 1979, Clark and colleagues[9] (once again including Reed) accepted this new variant, which they called ALM. Both working groups summarized in tabular form the histologic features of this new variant and the differences between it and the 2 forms defined earlier; these tables are reproduced in Tables 9 and 10 of the present article.

The first aspect evaluated in these 4 tables was usually the growth pattern of the tumor cells within the epidermis. Clark et al[3] used the term "pagetoid distribution" (single cells, nests, and masses) in SSM and compared this to a gradual increase in the number of basal melanocytes until they "virtually replace the basal keratinocytes" in LMM. Clark and Mihm[4] assert that pagetoid distribution is common in SMM and rare in LMM. Arrington et al[6] contrast the pagetoid growth pattern in SSM to the lentiginous pattern in LMM and plantar lentiginous melanoma. Clark et

Table 8 Clinical Characteristics and Outcomes of the 27 Cases of Plantar Melanoma with a Radial Component Studied by Arrington et al[a]

Sex	16 M/11 F		
Mean age at diagnosis, y	63.4		
Mean duration of lesions, mo	30.6		
Size, cm	2.7 (0.4–6.0)		
		Deaths from melanoma, n	
Level	II	2	0
	III	9	7
	IV	6	6
	V	10	5
	Total	27	18

Abbreviations: M, male; F, female.
[a]Data derived from Arrington et al.[6]

Table 9 Histologic Features of Melanomas With a Radial Component According to Arrington et al[a]

	SSM	LMM	PLM
Pattern	Pagetoid	Lentiginous	Lentiginous
Shape of melanocytes in epidermis	Epithelioid	Spindle and epithelioid	Spindle, epithelioid, and bizarre
Atypia of melanocytes	Uniform	Variable	Variable
Dendritic processes	Not prominent	Prominent	Prominent
Epidermal invasion	Prominent	Not prominent	Occasionally prominent
Epidermis	Hyperplastic	Atrophic	Markedly hyperplastic
Papillary dermis	Widened and inflamed	Normal thickness	Widened and inflamed
Usual shape of infiltrating melanoma cell	Epithelioid	Spindle	Spindle and epithelioid
Actinic damage in dermis (occasional, invariable, or absent)	Occasionally present	Invariably present	Absent

Abbreviations: LMM, lentigo maligna melanoma; PLM, plantar lentiginous melanoma; SSM, superficial spreading melanoma.
[a]Source Arrington et al.[6]

Table 10 Comparative Histologic Features of the Radial Growth Phases of Superficial Spreading, Lentigo Maligna, and Acral Lentiginous Types of Melanoma according to Clark et al[a]

	SSM	LMM	ALM
Location of melanoma cells within the epidermis	All epidermal layers	Basilar region	Basilar region
Cytology of the individually disposed intraepidermal melanocytes	Uniformly large epithelioid cells without prominent dendrites	Pleomorphic "normal" and bizarre melanocytes mixed. Dendrites inconspicuous	Uniformly large with prominent, complex dendrites
Histology of the intraepidermal nests of melanocytes	Nests quite large frequently bridging the entire thickness of the epidermis	Nests may be ellipsoidal in outline with the long axis tending to parallel the epidermal surface	Nests tend to bulge into dermis.
Cytology of the melanocytes forming the intraepidermal nests	Uniformly large epithelioid cells form the nests.	Cells are pleomorphic, some quite small, others large and bizarre.	Cells tend to be spindle-shaped and may be epithelioid
Invasion of the papillary dermis	Easily demonstrated	Essentially absent	Present, but may require search to find it
Solar changes in connective tissue	Variable	Present	Absent
Host response of lymphocytes and macrophages	Usually well developed	Minimal to absent	Present and prominent with extension into epidermis

Abbreviations: ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma.

[a]Source Clark et al.[9] The only difference between this table and the original is the order of the columns (in the original the order was ALM, LMM, and SSM). This change was made to ensure that all the tables in the present article followed the same order (SSM, NM, LMM, ALM) to facilitate comparisons.

Table 11 Cytology of the Intraepidermal Melanocytes in Each Type of Melanoma According to Different Papers

	SSM	LMM	ALM[a]
Clark et al[3]	Epithelioid	?	-
Clark and Mihm[4]	Epithelioid	Spindle-shaped with scant cytoplasm	-
Arrington et al[6]	Epithelioid without prominent dendrites	Spindle-shaped and epithelioid cells with prominent dendrites	Spindle-shaped, epithelioid, and bizarre cells with prominent dendrites
Clark et al[9]	*Individual cells*		
	Epithelioid without prominent dendrites	Normal to bizarre, without conspicuous dendrites	Epithelioid cells with prominent dendrites
	In Nests		
	Epithelioid	From small to large and bizarre	Spindle-shaped or epithelioid cells

Abbreviations: ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; SSM, superficial spreading melanoma.

[a]Plantar lentiginous melanoma in the terminology used by Arrington.

al[9] do not use the same terms, but do use equivalents when they say that atypical melanocytes are found throughout all the layers in SSM and only in the "basilar" region in LMM and ALM (plantar lentiginous melanoma according to Arrington's terminology).

It appears, therefore, that the 4 tables are consistent in this respect and that we can summarize by saying that SSM is characterized by a *pagetoid pattern* whereas in LMM and ALM proliferation is said to be *lentiginous*.

And what are they like, the tumor cells that proliferate in this way within the epidermis? In general, the authors cited above assess the characteristics of these cells both collectively and individually. When considering the cells collectively, they evaluate whether the melanocytes constitute a more or less uniform group or whether the population is essentially heterogeneous. Clark et al[3] (Table 2) found the melanocytes in SSM to be uniformly atypical (that is, all of them were "equally bad"). In LMM, on the other hand, they found the population to be extremely varied in shape and they use the term cell pleomorphism. Clark and Mihm[4] used the same terms, while Arrington et al[6] talk about uniform melanocytic atypia in SSM and variable atypia in LMM and plantar lentiginous melanoma (Table 9). In the later paper, Clark et al[9] asserted that the atypical melanocytes were uniformly large in SSM and ALM as opposed to pleomorphic in LMM, and that in ALM when the melanocytes formed nests the cells could be spindle-shaped or epithelioid (Table 10).

There appears to be an inconsistency between Tables 9 and 10 concerning this aspect of the cytology of melanoma (in Table 9, the cytology of plantar lentiginous melanoma is variable, while in Table 10 the cytology of ALM—the equivalent form—is uniform). Apart from this contradiction, however, the terminology used is largely the same: in some cases, the atypical melanocytes are similar or uniform and in others the atypia is variable or pleomorphic. We can, therefore, adopt the terminology of *uniform atypia* as opposed to *pleomorphic atypia*.

Together with this collective evaluation of the cytology we also find a description of the individual cells. In the case of SSM, Clark et al[3] repeatedly cite the presence of epithelioid melanocytes with abundant cytoplasm and dusty melanin granules. In LMM, however, they describe the melanocytes as pleomorphic and say that "some appear essentially normal" while "others have large nuclei or may be multinucleated." From this we deduce (although they do not explicitly say as much) that the cytoplasm of these cells is scant with respect to the nucleus. Clark and Mihm[4] are more explicit and describe large, predominantly epithelioid cells with abundant cytoplasm and large nuclei in SSM, and large, predominantly spindle-shaped cells with scant cytoplasm and large nuclei in LMM. Arrington et al[6] talk about epithelioid melanocytes without prominent dendrites in SSM, spindle-shaped and epithelioid melanocytes with prominent dendrites in LMM, and spindle-shaped, epithelioid, and atypical melanocytes, also with prominent dendrites, in plantar lentiginous melanoma. According to Clark et al,[9] the isolated intraepidermal melanocytes are epithelioid and without dendrites in SSM, normal to bizarre without conspicuous dendrites in LMM, and in ALM they are uniformly large with prominent dendrites and the cells that form nests tend to be spindle-shaped although they can be epithelioid.

With respect to the cytology of the single cells found in the intraepidermal component of melanomas, there appears to be a considerable difference of opinion among the different authors. The only feature common to all the accounts is that the melanocytes of SSM are epithelioid, that is, they have abundant cytoplasm and no dendrites. According to Clark and Mihm[4] the melanocytes in LMM—when not almost normal—have a large nucleus and scant cytoplasm and are predominantly spindle-shaped. However, Arrington et al[6] describe these cells as spindle-shaped and epithelioid with prominent dendrites, and Clark et al[9] describe them as normal to atypical, without conspicuous dendrites. Arrington et al[6] describe the atypical melanocytes of plantar lentiginous melanoma as spindle-shaped and epithelioid with prominent dendrites, whereas Clark et al[9] describe these cells as uniformly large with prominent dendrites when isolated but tending to be spindle-shaped when they are clustered in nests, although the cells in nests can also be epithelioid. These differences are summarized in Table 11 for greater clarity.

We can summarize this table by saying that Arrington et al[6] found only slight differences between LMM and ALM, whereas Clark et al[9] found differences, even though it is impossible to arrive at a simple conclusion because of the variability of the cell morphology within each type. However, if we confine ourselves to the repetition of the term spindle-shaped with respect to LMM (Clark and Mihm[4] and Arrington et al[6]) and to the terms epithelioid and spindle-shaped when talking about ALM (Arrington et al[6] and Clark et al[9]), we can conclude that the predominant cytology in each variant of melanoma may be *epithelioid* in SSM, *spindle-shaped* in LMM, and both in ALM. In the case of dendrites, these appear to be *absent* in SSM, *present* in ALM and, at least, *variable* in LMM.

Clark et al[3] and Clark and Mihm[4] contrast the frequent (almost constant) presence of *intraepidermal nests* (at times very large) of atypical melanocytes in SSM with the scant presence (or lower frequency) of such nests in LMM. Arrington et al[6] do not assess this aspect (Table 9), while Clark et al[9] describe separately, although with few differences, the cytology of the isolated atypical melanocytes and that of the melanocytes grouped into nests. They do not, however, report on the frequency with which nests appear in each one of the 3 melanoma subtypes (Table 10). With respect to the size and shape of the nests, those found in SSM are described as quite large ("frequently bridging the entire thickness of the epidermis"), while in LMM they "may be ellipsoidal in outline with the long axis tending to parallel the epidermal surface," and in ALM they "tend to bulge into the dermis" (Table 10). It is difficult to compare these 3 descriptions since the first refers to size, the second to shape, and the third to the location of the nest. Extrapolating from the information provided, we could say that the nests found in LMM and ALM are not usually large, and that those found in SSM and ALM are not usually ellipsoidal in outline or horizontal (and will therefore tend to be rounded). Likewise, we can deduce that in SSM and LMM the nests do not usually bulge into the dermis and will therefore tend to be located within the stratum spinosum. We have tried to summarize this information in Table 12.

Only Arrington et al[6] assessed the *epidermis*, which they found to be hyperplastic in SSM, atrophic in LMM, and very hyperplastic in plantar lentiginous melanoma.

Table 12 Characteristics of the Intraepidermal Nests of Melanomas According to the Authors Cited[a]

	SSM	LMM	ALM
Number	More common	Less common	?
Size	Large	Not large	Not large
Shape	Round	Ellipsoidal and horizontal	Round
Site	Not "hanging"[b]	Not "hanging"	"Hanging"

Abbreviations: ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; SSM, superficial spreading melanoma.

[a]Data derived from Clark et al,[3] Clark and Mihm,[4] Arrington et al,[6] and Clark et al.[9]

[b]Hanging = bulging into the dermis.

Table 13 Summary of the Structural and Cytologic Features of the Intraepidermal Component of Primary Nonnodular Cutaneous Melanomas According to Clark et al,[3] Clark and Mihm,[4] Arrington et al,[6] and Clark et al[9]

	SSM	LMM	ALM
Pattern	Pagetoid	Lentiginous	Lentiginous
Melanocytic atypia	Uniform	Pleomorphic	Uniform (Clark). Pleomorphic (Arrington)
Predominant cytology	Epithelioid	Spindle-shaped	Epithelioid and spindle-shaped
Dendrites	Absent	Variable	Prominent
Nests			
Number	Very common	Less common	?
Size	Large	Not large	Not large
Shape	Round	Ellipsoid and horizontal	Round
Site	Not "hanging"[a]	Not "hanging"	"Hanging"
Epidermis	Hyperplastic	Atrophic	Very hyperplastic
Actinic damage to the dermis	Occasional	Present	Absent

Abbreviations: ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; SSM, superficial spreading melanoma.
[a]Hanging = bulging into the dermis

Table 14 Summary of the Structural and Cytologic Features of the Intraepidermal Component of Primary Nonnodular Cutaneous Melanomas According to Clark et al,[3] Clark and Mihm,[4] Arrington et al,[6] Clark et al,[9] and Clark et al[10,a]

	SSM[b]	LMM	ALM
Pattern	Pagetoid. *Not exceptionally, basal band 1-4 cells thick*	Lentiginous	*Lentiginous. Sometimes pagetoid*
Melanocytic atypia	Uniform	Pleomorphic. *Slightly pleomorphic*	Uniform (Clark). Pleomorphic (Arrington)
Predominant cytology	Epithelioid	Spindle-shaped	Epithelioid and spindle-shaped
Dendrites	Absent	Variable. *Absent*	Prominent
Nests			
Number	Very common	Less common. *Common*	*Scant?*
Size	Large	Not large	Not large
Shape	Round	Ellipsoidal and horizontal	Round
Site	Not "hanging"[c]	Not "hanging." *"Hanging"*	"Hanging"
Epidermis	Hyperplastic	Atrophic	Very hyperplastic
Actinic damage to the dermis	Occasional	Present. *Moderate to severe*	Absent

Abbreviations: ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; SSM, superficial spreading melanoma.
[a]The words in italics are features reported by Clark et al in 1990[10] that differ from those described in his earlier papers (see Table 13).
[b]This pattern is uncommon in melanoma in situ.[10]
[c]Hanging = bulging into the dermis

Neither Clark et al[3] nor Clark and Mihm[4] assessed actinic damage in the dermis. However, after Arrington et al[6] published their assessment of actinic damage, Clark et al[9] also evaluated this aspect. Both groups found actinic damage to be occasional or variable in SSM, always present in LMM, and invariably absent in ALM.

Table 13 summarizes all the above findings.

In order to check whether Clark and his group subsequently changed, clarified, or refined any of the criteria they had defined between 1969 and 1979, we reviewed chapter 49 (entitled Dysplastic Nevus and Malignant Melanoma) of the book *Pathology of the Skin* edited by Farmer and Hood in 1990; Clark, Elder, and Guerry are the authors of the chapter in question.[10]

In this chapter, the description of the histology of SSM is similar to that published in the earlier articles, with 2 exceptions:

1. "It is uncommon to see this distinctive pattern of melanoma [that of SSM] without invasion."[10]
2. "One important variant histology of this particular radial growth phase lacks the distinctive pattern of pagetoid intraepidermal growth [of SSM]. […] The melanoma cells are usually seen as a layer of contiguous cells at the dermoepidermal interface. […] More commonly there is a layer two to four cells thick separating the keratinocytic epidermis, above, from the dermis, below [...] frequently associated with effacement of the rete ridges." In such cases, the cells are "[...] somewhat smaller than those of the classic histologic picture. […] This variant pattern is commonly, but not exclusively, seen in lesions of the lower limbs."[10]

With respect to LMM, the authors once again refer to the "basilar" distribution of the abnormal cells. They state that:

> "[...] [the epidermis] may be of normal thickness, or atrophic, reflecting the cutaneous phenotype, solar damage, and the age of patients who develop this form of melanoma. The tumor cells are disposed in small nests, which extend down from the epidermis into the papillary dermis without overt invasion. […] The cells composing the nests tend to be small, slightly pleomorphic, and exhibit diminished cohesiveness. […] [The isolated single cells] may be numerous and almost contiguous but are often moderate in number and clearly separate from each other. [...] The dermis almost always shows moderate to advanced solar degeneration."[10]

In the case of ALM, they say:

> "The cells tend to be in the basilar epidermal region [...]. The individual cells may show well-preserved dendrites [...]. Epithelioid melanocytes are also seen and [...] may grow upward and be similar in appearance to superficial spreading melanoma."[10]

We see, in light of these descriptions, that we can make some modifications to Table 13 and add some details:

- The distinctive pattern of SSM is uncommon in melanoma in situ.
- An undetermined number of cases of SSM (but not a small number because this histological variant is commonly seen in the lower limbs, one of the main sites for melanoma, particularly among women) feature a distinctive lentiginous pattern that takes the form of a layer of contiguous cells at the dermoepidermal junction (which we call a basal frieze pattern).
- Melanocytic atypia is only slightly pleomorphic in LMM (whereas the presence of cell pleomorphism had, since 1969, been one of the characteristics that distinguished LMM from SSM).
- Dendrites are not characteristic of LMM.
- Nests are only rarely found in ALM.
- The nests in LMM are now described as "hanging" from the epidermis (extending down into the papillary dermis) whereas in previous papers this had only been a characteristic of ALM. Now, with respect to ALM, the authors only say that nests are rare.
- The thickness of the epidermis in LMM appears to be independent of the tumor and a consequence of other, essentially exogenous, factors.
- The severity of actinic damage in LMM is quantified, although logically such damage is a consequence of the site of the lesion and not of the melanoma itself.

Table 14 is a repetition of Table 13 with the addition, in italics, of the information that represents a divergence between the content of Table 13 and the later chapter by Clark et al.[10]

In light of the above, we can conclude that our attempts to determine the characteristics which, according to Clark and his colleagues, allow us to differentiate with some precision between one type of nonnodular melanoma and another has failed: the distinctive pattern of SSM is uncommon and, furthermore, a new pattern has been identified that takes the form of a basal layer of cells 2 to 4 cells thick in a frieze pattern. In other words, the most common type of melanoma (>60%) often lacks any unique histologic characteristics. With respect to the other 2 subtypes (LMM and ALM), only the thickness of the epidermis and the presence or absence of actinic damage to the dermis are said to be conclusive, but both these characteristics are a consequence of the site of the lesion and not of the melanoma itself.

In view of this failure to establish a histologic classification we must, as Elder et al[8] stated in 1978, turn to the clinical picture. However, they do not tell us how to do this. When does histology override the clinical findings? When is the clinical presentation more important than histology? When 1 of the 2 predominates over the other? Which cases can be considered unclassifiable when we have no clear classification criteria?

A subsequent review of the bibliography discussed above led us to identify further contradictions which we had previously overlooked.

1. In the case series that formed the basis of the first article by Clark et al[3] none of the cases were described as unclassifiable or difficult to classify. Of the 209 cases studied, 32% were NM, 54% were SSM, and 14% were LMM (Table 4).
2. The classification, as the authors explained, was definitively histologic:

   > "It is the evaluation of these superficial cells that determines the classification of melanoma" [...].[3]

   Although they concluded that LMM appears "usually on the exposed surfaces of the elderly,"[3] the authors do not take site into account as a factor differentiating SSM from LMM:
   - Of the 51 melanomas of the scalp and neck, 18 were SSM and 25 LMM.
   - 4 LMM were located on the limbs: 2 on the forearm and the dorsum of the hand and 2 on the legs.[3]
3. They also concluded that lentigo maligna melanoma was "a slowly growing, relatively benign neoplasm [...]."[3] However, if we look more closely at Table 4, we see that the supposed benign nature of LMM is not supported by their data since the percentage of disease-free survivors of SSM (46.5%) does not differ significantly from that of disease-free survivors of LMM (55.2%). Moreover the 8.7% difference can be accounted for by the fact that the mean follow up was 6 years in SSM and only 4.75 years in LMM. Years later, Koh et al[11] (with Clark and Mihm among the coauthors) rectified this assertion that LMM is a relatively benign neoplasm when they found the prognosis to be the same for LMM as for other types of melanoma of the same thickness.
4. But the detail in this first article[3] that particularly claimed our attention was that 6 of the 209 melanomas were located on the palm, 25 on the soles, and 4 in the nail bed. Of these 35 cases, 20 were classified as SSM and 15 as NM (none as LMM).

   Eight years later when Arrington et al[6] studied plantar melanomas, they highlighted the marked histologic

similarity between such cases and lentigo maligna and concluded that:

> "[a] nonactinic lentiginous variant [of melanoma] occurs on the palms and soles, the subungual areas, the muco-cutaneous junction of the oral and nasal cavities, and the anus."[6]

Those authors used the term "plantar lentiginous melanoma" to designate such cases.[6]

Two years later, Clark, Bernardino, Reed, and Kopf[9] integrated plantar lentiginous melanoma into the broader concept of ALM, a designation that included melanomas of the palms, soles of the feet, nail bed and mucous membranes, since:

> "malignant melanomas of the superficial spreading and nodular varieties occur uncommonly in the volar and subungual sites."[9]

In the case series studied 8 years earlier, all the cases of melanoma affecting the palms, soles, and nail bed (35 cases) were classified as either nodular (15 cases) or superficial spreading melanoma (20 cases).[3]

5. Another interesting fact that can be gleaned from the data shown in Table 4 is that the patients with LMM are significantly older than the other 2 groups of patients. This is the finding that gave rise to the conclusion in the article cited that lentigo maligna melanoma "was a slowly growing, relatively benign neoplasm usually on the exposed surfaces of the elderly."[3]
However, the average age in the group of 27 patients with plantar melanoma studied by Arrington et al[6] was 63.4 years, and this finding has been clearly confirmed by later studies.[12-14] In other words, LMM is not differentiated from other melanomas in terms of prognosis[11] and nor is it differentiated from ALM by either age of onset,[6,12-14] or structural pattern (lentiginous in both cases).[6,9]
6. In the same book[7] that includes the study by Clark et al[9] on ALM, Elder, Ainsworth, and Clark[8] assert that:

> "Difficulty may be encountered from time to time in histologic distinction among the various forms of melanoma categorized above, but if clinical as well as histologic parameters are assessed, differentiation is not usually a problem."[8]

They do not, however, explain which clinical parameters should be taken into account in cases that are difficult to classify on the basis of histology: site, age, morphology of the lesion, rate of evolution?

7. Ten years later, Clark, Elder, and Guerry[10] told us that the distinctive histologic pattern of SSM is uncommon in the absence of invasion, in other words, in melanoma in situ, and that, in addition, other cases of SSM lack the "distinctive pattern of pagetoid intraepidermal growth" even during the radial growth phase. They go on to say that the radial growth phase is characterized by the horizontal plaque-like growth that we call a "basal frieze pattern," which they describe in detail. Nevertheless, they do not explain which patterns they find in those melanomas in situ that do not present the distinctive SSM pattern, but which they, nonetheless, classify as SSM, leading us to pose the question: On what basis do they make such a classification?

Conclusions

- NM is only distinguished from SSM by the number of ridges affected by the in situ component: if 3 or less ridges are affected, disease is classified as NM and if 4 or more are affected, as SSM.
- LMM and ALM are only differentiated by site: if the melanoma affects the palms, soles, nail bed, or semimucosal membranes, it is ALM, if it occurs in any other part of the body, it is classified as LMM.
- The distinctive pagetoid pattern of SSM is uncommon in melanoma in situ.
- A not insignificant number of cases of SSM are characterized by a distinctive horizontal lentiginous growth pattern, which we call a basal frieze pattern.

This historical review of Clark's supposed classification of cutaneous melanomas arose when one of our group (MH) attempted to classify[15] 331 cases of melanoma using Clark's criteria in the course of a doctoral thesis. After many dead ends and returns to square one, we were amazed to discover that Clark's criteria did not in fact really exist or, more precisely, that they had changed over time and, even more worrying, had been progressively diluted.

Once it had been established that melanomas affecting the least exposed areas of our skin—the soles of the feet—were similar to those of the face in both clinical and histologic morphology and with respect to age of onset and prognosis, the attempt to classify melanomas using Clark's criteria should have been abandoned forthwith. The only category still extant at this point was SSM, but even Clark[8,10] himself progressively questioned and doubted the histologic uniqueness of this category.

After this review of the history of this classification, our response to the question posed in the title of this article must be that yes, in 1967-1968 Clark et al[2-4] classified cutaneous melanomas into 3 groups—MN, SSM, and LMM—but that in succeeding years after this the same group of authors dismantled the classification piece by piece.[8,10] What remains inexplicable is why most authors, with a few exceptions,[16-20] have continued to use Clark's classification system in their papers to the present day.

We believe that it was the identification of LMM, thought to be a type of melanoma with distinctive clinical characteristics (slow growing with a long in situ phase and frequent zones of regression, late onset in photoexposed areas of the body and supposedly with a better prognosis), that led Clark and his colleagues to attempt to draw up a classification with prognostic implications. However, as we have seen, many melanomas affecting nonphotoexposed areas (the soles of the feet) have the same clinical and histologic (lentiginous) features supposedly characteristic of LMM, and at the same thickness there is no difference in prognosis between the 2 variants.

When this fact was established in 1984,[11] the classification system first devised in 1964 by Clark should have been

abandoned.[2] Recent studies appear to indicate that melanomas will in future be classified on the basis of genetics and molecular biology.[21] We encourage our readers to never lose their critical sense when evaluating new hypotheses as we believe most clinicians did when evaluating Clark's supposed system for classifying melanomas.

Conflict of Interest

The authors declare no conflicts of interest.

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