

Melanocytes in Long-standing Sun-Exposed Skin

Quantitative Analysis Using the MART-1 Immunostain

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Objective: To help distinguish early melanoma from normal sun-damaged skin by quantifying the density, confluence, and depth of follicular penetration of melanocytes in long-standing sun-exposed skin of the face and neck.

Design: Case series.

Setting: Referral center.

Patients: Random selection of 149 patients undergoing Mohs surgery for basal cell and squamous cell carcinomas of the face and neck.

Intervention: Frozen-section slides were made from long-standing sun-exposed normal skin and stained with MART-1 (melanoma antigen recognized by T cells 1 staining) immunostain.

Main Outcome Measures: The number, confluence, and depth of penetration of melanocytes along the follicular epithelium were quantified per high-power field (original magnification $\times 400$, equivalent to 0.5 mm of skin). Confluence was categorized by the

number of adjacent melanocytes (none, 0-1; mild, 2; moderate, 3-6; and severe, >6).

Results: The mean number of melanocytes per high-power field was 15.6 (range, 6-29). Confluence was severe in 1.0% of the specimens, moderate in 34.0%, mild in 54.0%, and absent in 11.0%. Focal areas of increased melanocyte density occurred in 24.2% of the specimens; in these areas, the mean number of melanocytes per high-power field was 20.3 (range, 7-36) and the confluence of melanocytes was severe in 13.0%, moderate in 50.0%, and mild in 37.0%. The mean depth of follicular epithelium penetration by melanocytes was 0.38 mm. Pagetoid spread and nesting of melanocytes were not seen. Nonspecific scattered MART-1-staining dermal cells were in half of the slides.

Conclusions: Melanocytes in long-standing sun-exposed skin have an increased density and a confluence that is often moderate (3-6 adjacent melanocytes), but they do not exhibit pagetoid spread or nesting. Nonspecific MART-1-staining dermal cells should not be interpreted as invasive melanoma.

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PHYSICIANS WHO DIAGNOSE melanoma histologically or who evaluate the surgical margins of melanoma often face the difficulty of distinguishing nonmalignant melanocyte hyperplasia from melanoma in situ in sun-damaged skin (ie, lentigo maligna [LM]). Lentigo maligna and LM melanoma (LMM) are characterized by hyperplasia of atypical melanocytes occurring singly or in nests, exhibiting pagetoid spread and extending down the hair follicles. Many of these criteria overlap with the changes seen in skin damaged from long-term exposure to the sun.¹ Because there are no well-defined criteria for melanocyte density in sun-damaged skin, the distinction between benign and malignant is often arbitrary. The penetration of melanocytes along the follicular epithelium is considered characteristic of LM and LMM, yet the depth of penetration in long-standing sun-exposed skin of the face and neck is un-

known. With such uncertainties, many physicians most likely err on the side of overdiagnosing melanoma in sun-damaged skin to avoid the obvious medical and legal consequences of not diagnosing true melanoma. Overdiagnosis, however, leads to additional and unnecessary surgery, morbidity, and deformity.

Several previous studies have attempted to address this issue. In a study of 84 patients, Fallowfield et al² found that sun-exposed forearm skin had 27 to 55 melanocytes per 200 keratinocytes and buttock skin had 10 to 35 melanocytes per 200 keratinocytes. In this study, S100 immunostains were used in specimens from fewer than half of the patients.² By using immunohistologic staining with MART-1 (melanoma antigen recognized by T cells 1 staining), Kelley and Starkus³ found that sun-protected skin had a melanocyte-keratinocyte ratio of approximately 1:10 in 5 patients. In our experience, there are

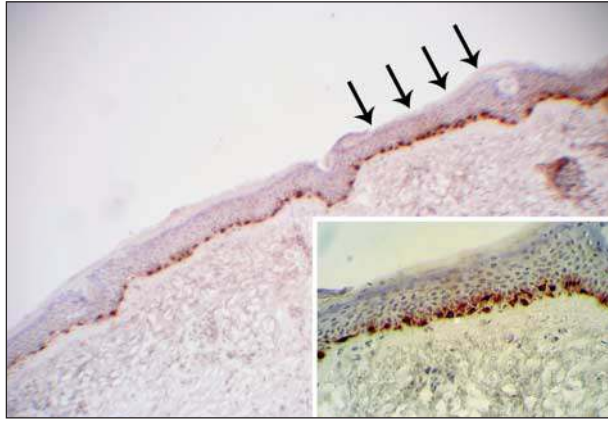


Figure 1. Typical melanoma antigen recognized by T cells 1–staining normal sun-exposed skin with a focal area of increased melanocyte density (arrows) (original magnification $\times 200$). Inset, High-power view of the focal area of increased melanocyte density showing nearly confluent melanocytes (melanoma antigen recognized by T cells 1 stain, original magnification $\times 400$).

50 to 70 keratinocytes per high-power field (original magnification $\times 400$); therefore, 5 to 7 melanocytes per high-power field would be present in sun-protected skin. In the same study by Kelley and Starkus, sun-damaged skin from 9 patients had “practically confluent” melanocytes. Long-term exposure to UV-B irradiation has been shown to increase the number of melanocytes in the epidermis.⁴

The goal of the present study was to define, in a clinically useful manner, the number, degree of confluence, and depth of penetration of melanocytes in long-standing sun-exposed skin of the head and neck.

METHODS

Patients undergoing Mohs surgery for basal and squamous cell carcinoma of the head and neck were randomly selected during a 5-month period (December 1, 2003–April 30, 2004). For each of the 149 patients selected for the study, the patient’s age, sex, type of tumor excised, personal history of dysplastic nevi or malignant melanoma, and history of recent intense sun exposure were recorded. Recent intense sun exposure was defined as outdoor exposure, within 2 weeks before surgery, in a sunny climate such as that of Florida, which is in contrast to the climate of western Pennsylvania (particularly in the winter), where most study participants lived. Recent intense sun exposure was of interest because it increases the number and activity of melanocytes.⁵

After the tumors were completely removed, the proposed dog-ears to be excised during reconstruction were evaluated for the presence of any visible lesions (ie, ephelides, lentigo, seborrheic keratosis, or nevi). Dog-ears were excluded from the study if a skin lesion was present or if the patient had a history of irradiation to the face or neck. From the remaining dog-ears, 1-cm strips of skin were cut, defatted, and prepared for vertical frozen sections. Particular attention was paid to cutting the tissue into thin sections (3–4 μm), which is technically easier after defatting the tissue. Each slide had an average of 3 tissue sections. The slides were stained with MART-1 immunostain using a described protocol.⁶ In this protocol, the secondary antibody is bound to a spherical polymer with attached horseradish peroxidase, which activates the bronze-colored diaminobenzidine chromogen. Compared with traditional immunostaining protocols, the use of the polymer makes this protocol more efficient and provides a more powerful amplification of the chromogen.⁶ Of

the 149 patients, 17 were excluded from the study owing to poor MART-1 staining of tissue, lack of epidermis on the slide prepared, or the presence of architectural changes of a lentigo along the entire epidermis. One slide from each of the remaining 132 patients was included in the study.

The slides were examined microscopically (high-power field, $\times 400$ magnification, equivalent to 0.5 mm of skin) for number, density, confluence, and depth of melanocytes in the follicular epithelium. Measurements of melanocytes in 0.5 mm of skin have been accurate in distinguishing sun-damaged skin from melanoma in situ.⁷ On each slide, a representative area was chosen. This was 0.5 mm of epidermis that had a melanocyte density similar to the remainder of the slide. Areas with histologic evidence of a lentigo were avoided. Density and confluence measurements were made from epidermis that was flat or had the least undulations with respect to the horizontal axis. Thick sections were not used because overlapping melanocytes may give the appearance of increased melanocyte density. To avoid counting melanocytes that were not in the same plane, only the melanocytes in focus were counted. If there was marked variability of density and confluence on a slide, measurements were made in a representative area and in areas of increased melanocyte density. Epidermal melanocyte confluence was stratified as none, mild (2 adjacent melanocytes), moderate (3–6 adjacent melanocytes), or severe (>6 adjacent melanocytes). In slides with follicles, the depth of the deepest melanocyte penetrating the follicular epithelium was measured from the granular layer of adjacent epidermis. Melanocytes in the papillae of the follicle were not counted. The confluence of the melanocytes in the follicular epithelium was stratified with the same scale used for epidermal confluence. The presence of pagetoid spread and melanocyte nest (≥ 4 clustered melanocytes), if any, was noted.

Mean \pm SD and medians were calculated for the density, degree of confluence, and depth of follicular penetration of melanocytes. Factors that may affect melanocyte density (age, history of dysplastic nevi or melanoma, and recent intense sun exposure) were noted. A Kruskal-Wallis 1-way analysis of variance was used to compare the average density between subgroups of patients.

RESULTS

All 132 patients were white. Of these 132 patients, 116 (87.9%) had basal cell carcinoma, 12 (9.1%) had squamous cell carcinoma, 2 (1.5%) had atypical fibroxanthoma, 1 (0.8%) had a sebaceous tumor, and 1 (0.8%) had a vascular tumor (percentages total >100 because of rounding). The mean age of the patients was 70 years (range, 32–98 years); 54.0% were men, and 46.0% were women. All the skin samples were from sun-exposed areas of the head or neck. Eleven patients had a history of recent intense sun exposure, and 5 had a personal history of dysplastic nevi or melanoma.

The mean number of melanocytes per high-power field was 15.60 ± 4.38 (median, 15.0; range, 6–29) (Figure 1). Melanocyte confluence was severe in 1.0%, moderate in 34.0%, mild in 54.0%, and absent in 11.0% of the patients. There were focal areas of increased melanocyte density in 32 (24.2%) of the 132 slides. In these areas, the mean number of melanocytes per high-power field was 20.3 ± 5.2 (median, 20; range, 7–36) (Figure 1, inset). The confluence of melanocytes in these areas of increased melanocyte density was severe in 13.0%, moderate in 50.0%, mild in 37.0%, and absent in 0% of the patients. In slides with

severe melanocyte confluence, the number of adjacent melanocytes did not exceed 9. There was no pagetoid spread or nesting of melanocytes in the epidermis.

In 120 of 132 slides, at least 1 complete hair follicle was present. The mean depth of the deepest melanocyte in the basal layer of the follicular epithelium was 0.38 ± 0.04 mm (range, 0-1.5 mm) (**Figure 2**). The confluence of melanocytes in the follicular epithelium

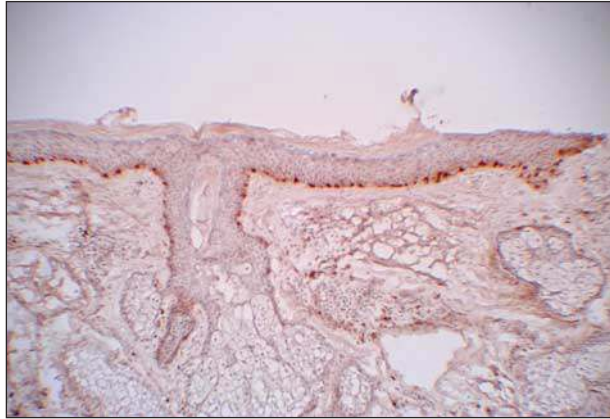


Figure 2. Melanoma antigen recognized by T cells 1–staining normal sun-exposed skin shows extension of melanocytes along the follicle (original magnification $\times 200$).

was severe in 0%, moderate in 18.0%, mild in 53.0%, and absent in 29.0% of the patients.

There was no statistically significant difference in the measured variables among patients with a history of recent sun exposure and malignant melanoma or dysplastic nevi compared with all other patients ($P < .05$). There was a statistically significant ($P < .001$) inverse correlation between average melanocyte density and patient age.

Scattered dermal MART-1–staining cells were observed in the dermis in about half of the slides (**Figure 3**). These cells were more likely to be present in slides with some background staining and adjacent to torn edges of tissue. In most slides, these cells were faintly stained and were scattered within the dermis without nesting. In a few slides, they were darkly stained without features of nesting. Three patterns of dermal staining were noted: inflammatory, follicular, and dendritic. These cells also stained after repeating the MART-1 immunostain protocol without the MART-1 antibody.

COMMENT

The goal of this study was to quantitatively define the density, confluence, and depth of follicular penetration of melanocytes in long-standing sun-exposed skin of the

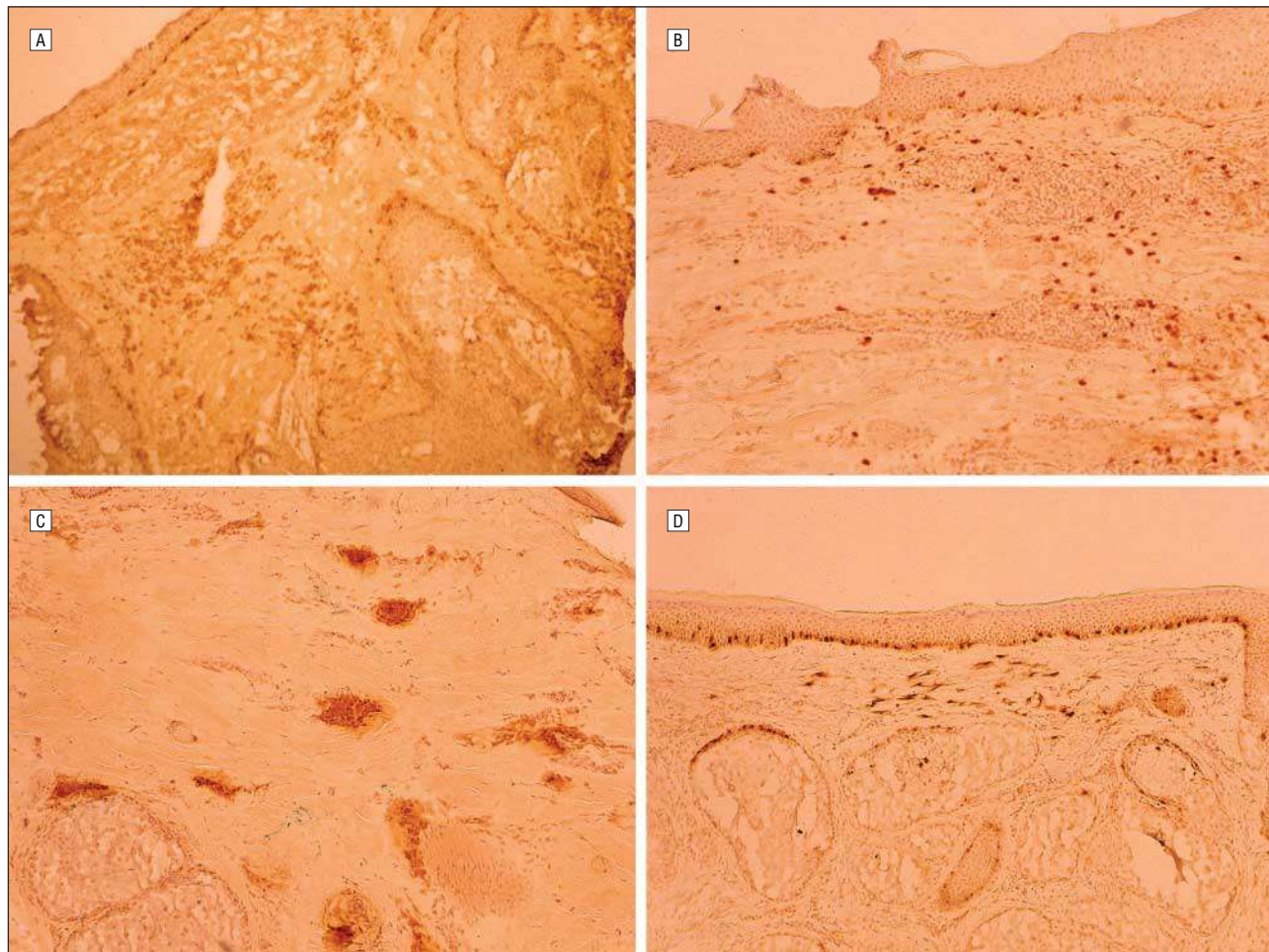


Figure 3. Nonspecific melanoma antigen recognized by T cells 1–staining dermal cells in an inflammatory pattern (original magnification $\times 200$) (A and B), a follicular pattern (original magnification $\times 200$) (C), and a dendritic pattern (original magnification $\times 200$) (D).



Figure 4. Normal skin cut tangentially, simulating pagetoid spread of melanocytes. Tangentially cut tissue typically has thicker stratum corneum than surrounding tissue (melanoma antigen recognized by T cells 1 stain, original magnification $\times 400$).

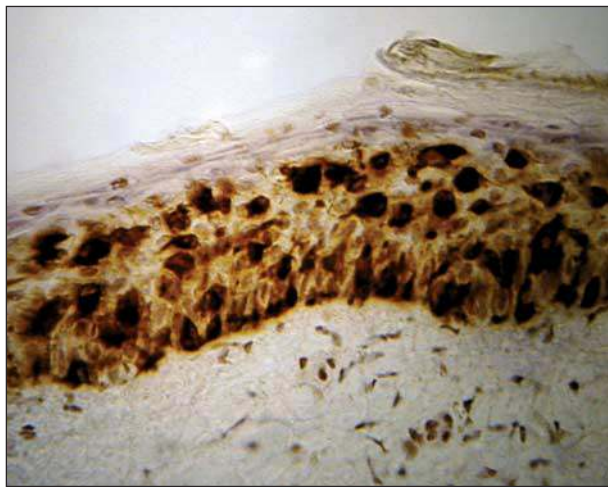


Figure 5. Malignant melanoma in situ, with vertical stacking of melanocytes in the epidermis (melanoma antigen recognized by T cells 1 staining, original magnification $\times 400$).

head and neck. This is important because it is not known how much melanocyte hyperplasia is needed to diagnose LM and LMM. Without quantitative guidelines for the normal density of melanocytes in sun-damaged skin, decisions about the histologic diagnosis and margins of melanoma in sun-exposed skin are made subjectively. By better defining normal features in practical and easily applicable terms, we hope to provide the evidence to aid physicians faced with this dilemma.

We found that normal long-standing sun-exposed skin has an average of 15 to 20 melanocytes per high-power field (in 0.5 mm of skin), a confluence of up to 9 adjacent melanocytes, and melanocytes extending along hair follicles. However, there was no nesting or pagetoid spread of melanocytes. Although tissue that is cut tangentially may seem to have high-level melanocytes in the epidermis, this should not be confused with pagetoid spread (**Figure 4**).

Our data are comparable with those of Acker and colleagues,⁷ who found a mean of 11.61 ± 1.98 melanocyte nuclei per 0.5 mm in sun-damaged skin in a morphometric study. They found that the mean number of mel-

anocyte nuclei in melanoma in situ, 37.83 ± 11.12 , was significantly higher.⁷

In another study, Weyers et al⁸ found that sun-exposed skin with melanocytic hyperplasia has a median of 10 and a maximum of 26 melanocytes per 0.5 mm. This data may be of limited value, as only 10 of the 50 cases of sun-damaged skin were studied immunohistochemically with HMB-45 and S-100 stains. In comparison, melanoma in situ had a median of 50 and a maximum of 134 melanocytes per 0.5 mm. They also found that the HMB-45 immunostain stains sun-damaged skin and melanoma in situ similarly. This is expected because this immunostain stains melanocytes (regardless of source), and sun-damaged skin is known to have a high density of melanocytes. It was the objective of the present study to better define the density, confluence, and depth of follicular descent of melanocytes in sun-damaged skin, so that benign melanocytic hyperplasia is not diagnosed as melanoma.

Melanocyte number alone should not be used to discriminate sun-damaged skin from early melanoma. The degree of confluence, nesting, and pagetoid spread are other crucial criteria. In our experience, "vertical stacking" of melanocytes in the epidermis is a common finding in melanomas (**Figure 5**).

In the present study, we also found that it is normal for melanocytes to extend along the follicular epithelium in sun-damaged skin. In their study, Weyers et al⁸ noted that melanocytes descended "far" down adnexal epithelial structures in only 12% of cases of sun-exposed skin with melanocytic hyperplasia, compared with 96% of cases of melanoma in situ. However, they did not quantify what percentage of sun-exposed skin had melanocytes with "short" descent down adnexal epithelium. Short descent was defined as not reaching "the level of the uppermost portion of sebaceous glands of surrounding follicles."^{8(p561)} Hence, melanocytes can be seen along the follicular epithelium of normal sun-exposed skin and melanoma in situ. Although melanoma in situ is likely to have deeper descent of melanocytes along the follicle, this feature alone should not be used to distinguish the 2.

An old argument for wide margins of excision for melanoma was the concept of field change in the epidermal melanocyte population surrounding a melanoma.⁹ However, our study and a previous study¹⁰ support the notion that field change may simply be the result of long-term sun exposure.

How do our data compare with data from sun-protected skin? Contrary to the long-held belief that the number of melanocytes in the skin is static,^{11,12} it has been established that sun exposure increases the number of melanocytes^{2,4,13-15} and that melanocyte density is proportional to cumulative sun exposure.¹⁵ Even casual sun exposure, without sunbathing, may induce maximal melanocyte proliferation.² After only 3 days of sun exposure, melanocytes become more dendritic and more dopa positive¹⁶; after 12 days, the number of melanocytes increases.⁵ The use of MART-1 immunostains has shown that sun-protected skin has a melanocyte-keratinocyte ratio of approximately $1:10^3$ (**Figure 6**).

The MART-1 protein is a transmembrane protein expressed by benign and malignant melanocytes.¹⁷ Shown to be more sensitive and specific than HMB-45 for mel-

noma and melanocytes in general,¹⁸ the MART-1 immunostain is a valuable tool in the evaluation of surgical margins of melanoma in sun-damaged skin. Melanocytes stain intensely and can be discriminated easily from keratinocytes in frozen sections, but it is important to have high-quality thin sections to minimize background chromogen coloration.

In a recent article by Shabrawi-Caelen et al,¹⁹ the authors raised the question regarding the specificity of the MART-1/Melan-A immunostain in sun-damaged skin. In their study of 10 cases of actinic keratoses, they found that samples stained with MART-1 had more immunoreactive cells than samples stained with S100 or HMB-45. They had 2 explanations for this: (1) MART-1 is more sensitive than the other immunostains and (2) MART-1 may also stain keratinocytes and other nonmelanocytic cells damaged by an inflammatory process, as suggested by Maize et al.²⁰ How does this affect our data? It is possible that some of the cells counted as melanocytes may actually have been keratinocytes. However, our results should be applicable to cases in which MART-1 is used to diagnose melanoma in sun-damaged skin. The MART-1 rapid immunostain protocol⁹ is the most practical and efficient method for the Mohs surgeon to better judge the presence or absence of melanoma at the surgical margin. Because we defined the upper limit of normal melanocyte density and confluence, our data should aid in preventing the overdiagnosis of positive surgical margins in the management of melanoma in sun-damaged skin. This holds true, especially in light of the data presented by Shabrawi-Caelen et al.¹⁹ However, special care is needed when what seem to be melanocytic nests are seen. "Pseudonests," which may be aggregates of keratinocytes, macrophages, and lymphocytes resulting from cellular damage along the dermal-epidermal junction, may be seen on hematoxylin-eosin- and MART-1-stained slides.²⁰

The finding of scattered MART-1-staining cells in the dermis of normal sun-exposed skin is also of concern. They seem to be nonspecific and can be seen even if the MART-1 antibody is withheld from the staining protocol. They were more likely to be present in slides with background staining or near torn edges of tissue. These nonspecifically staining cells may lead to the upgrading of the Breslow thickness of melanomas stained with MART-1 or to misinterpretation of an in situ melanoma as being invasive. These cells may be nonmelanocytic cells damaged by an inflammatory process, as suggested by Maize et al.²⁰ Although the identity of these cells is unclear, mislabeling them as melanocytes has tremendous implications in the care of patients with melanoma.

Atypical melanocytes and multinucleated ("starburst") melanocytes were not addressed in this study because they are not readily discernible in frozen sections; in addition, there is no uniform criterion for melanocyte atypia. Although atypical melanocytes are uniformly seen in melanoma, they are also seen in normal sun-exposed skin^{2,21} and should not be used alone as a criterion for melanoma.

Nearly all patients in this study were from western Pennsylvania and the surrounding regions. Only 11 patients had recent intense sun exposure. If a similar study were performed with patients who had recent intense sun exposure, the melanocyte density and confluence may

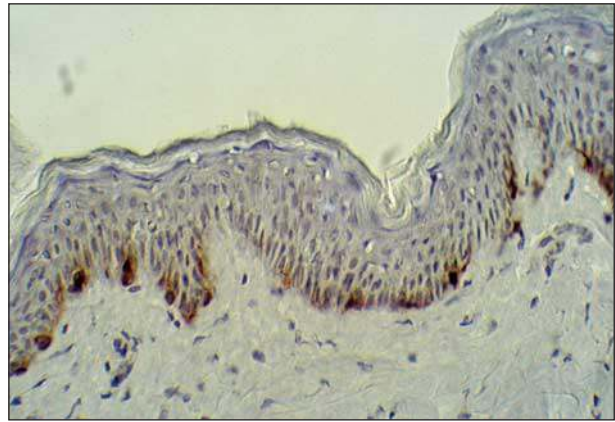


Figure 6. Sun-protected normal skin from the abdomen. Melanocyte confluence is absent (melanoma antigen recognized by T cells 1 staining, original magnification $\times 400$).

be even greater than in our study. The inverse correlation between melanocyte density and patient age may result from the natural maturation process of nevus cells.

There are essentially 3 ways to define histologic criteria to distinguish benign from malignant. The first is to study the histologic features of malignant tumors known to metastasize. This has been done for melanoma. In addition to the defined criteria, we have observed that in most melanomas there is vertical stacking of melanocytes in the lower half to two thirds of the epidermis, with or without pagetoid spread of melanocytes reaching the granular layer. The second way is to study the features of normal skin, which was the purpose of this study: to define quantitatively the features of normal skin in sun-exposed areas. The third way is to observe patients according to the criteria established from the previous 2 designs and to determine whether the biological behavior is in concordance with the histologic features. Previous work,²² which used confluent hyperplasia and nesting as criteria for Mohs excision of melanoma, resulted in recurrence of less than 0.5% in 535 patients with 5-year follow-up data; ie, not excising areas of increased melanocyte density (such as those found in the present study) did not lead to persistence or recurrence of melanoma. This further supports the clinical implications of this study in the care of patients with pigmented lesions in sun-exposed skin.

Data from the present study should assist the physician in discerning increased melanocyte density in sun-damaged skin from that in LM and LMM. The Mohs surgeon or pathologist has the evidence needed to avoid overdiagnosing melanoma in sun-exposed skin. The findings of increased melanocyte density and mild to moderate confluence alone do not substantiate the diagnosis of LM or LMM. There should be nesting, vertical stacking, or pagetoid spread. In addition, the finding of melanocytes along the follicular epithelium is normal in sun-damaged skin and is not specific to LM or LMM.

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