Melanocytic Proliferations Associated With Lichen Sclerosus

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Objectives: To describe the clinicopathologic features of melanocytic proliferations associated with lichen sclerosus (LS) and to compare these findings with those in controls.

Design: Cohort study.

Setting: Academic and private practice dermatology and dermatopathology services.

Patients: Cases of melanocytic proliferations associated with LS and consecutive controls with persistent (recurrent) melanocytic nevi, persistent malignant melanomas, and compound melanocytic nevi.

Main Outcome Measures: Diagnostic criteria and disease recurrence.

Results: Eleven patients, all female, with a mean age of 40 years (range, 8-83 years), presented with pigmented lesions clinically suspected to be malignant melanoma or atypical melanocytic nevi affecting the vulva (7 patients), perineum (3 patients), or chest (1 patient). Lichen sclerosus was first identified in the biopsy specimen and subsequently confirmed clinically. In 10 cases, a melanocytic nevus was superimposed on LS (overlying or entrapped by sclerosis), whereas LS was found at the periphery of vulvar malignant melanoma. After complete excision, no recurrences have been reported for the melanocytic nevi in LS (mean follow-up, 29 months; range, 4-60 months). Compared with control lesions, the LS melanocytic nevi most closely resembled persistent melanocytic nevi and could be distinguished from persistent malignant melanoma histologically. Melanocytes, nevoid or malignant, proliferating contiguously with fibrotic or sclerotic collagen, contained abundant melanin, diffusely expressed HMB-45, and had a higher Ki-67 labeling index than ordinary melanocytic nevi. However, persistent malignant melanoma exhibited mitotic figures, significantly higher Ki-67 labeling index, and deep dermal HMB-45 expression compared with LS melanocytic nevi and persistent melanocytic nevi.

Conclusions: Melanocytic nevi occurring in LS have features in common with persistent melanocytic nevi and can mimic malignant melanoma. An “activated” melanocytic phenotype is seen in LS melanocytic nevi, implicating a stromal-induced change.

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Melanocytes overlying scars exhibit an activated, regenerative phenotype manifested by HMB-45 expression and increased proliferation. In consequence, scars can exhibit clinical pigmentation or melanocytic hyperplasia. When the scar pigmentation is secondary to a persistent (“recurrent”) melanocytic nevus, the histologic findings can be striking and mimic those of malignant melanoma, thus the moniker “pseudomelanoma.” Keratinocytes overlying the dermal sclerosis in lesions of lichen sclerosus (LS) also manifest a regenerative phenotype. However, clinical pigmentation in LS is infrequent and melanocytic proliferations in LS are rare and difficult to interpret. In this study, we collected cases of melanocytic proliferations occurring in lesions of LS to determine their clinical pathologic characteristics and natural course. To more closely delineate the pathologic changes, we compared these LS-associated melanocytic lesions with ordinary compound (nondysplastic) melanocytic nevi, persistent melanocytic nevi, and persistent malignant melanoma.

RESULTS

CLINICAL FINDINGS

LS-Associated Melanocytic Proliferations

Eleven melanocytic proliferations were identified arising in a region of skin affected by LS (Table 1). These patients were all female, with mean age of 40 years (median, 31 years; range, 8-83 years). These pigmented lesions had a mean size of 6 mm (range, 2-18 mm) and involved the vulva...
PATIENTS AND METHODS

CASE SELECTION

Eleven cases (slides and blocks) with clinical data from pathology reports and clinical records of melanocytic proliferations (10 melanocytic nevi and 1 malignant melanoma) identified within a field of LS were retrieved from the consultation files of one of us (M.C.M.) (2 cases) and from the dermatology and/or dermatopathology services of others of us (J.A.C., 5 cases; A.N.C., 2 cases; K.W., 1 case; and V.G.P., 1 case) (Table 1). One case (patient 2) was described previously.11 For comparison, consecutive controls consisting of 12 recurrent or persistent melanocytic nevi, 7 incompletely excised or persistent malignant melanomas (4 in situ and 3 invasive), and 9 ordinary compound melanocytic nevi were retrieved from the files of the Albany Medical College Dermatopathology Service, Albany, NY. One additional case of persistent melanocytic nevi was found (by K.W.) in which dermoscopic examination had been performed.

Compound (ordinary) melanocytic nevi were selected on the basis of the absence of lamellar fibrosis or concentric eosinophilic fibrosis, lymphocytic infiltrates, fusion of rete ridges, or lateral extension of the junctional component—all features of so-called dysplastic melanocytic nevi.15

HISTOLOGIC ANALYSIS

Hematoxylin-eosin–stained slides from paraffin-embedded tissue were evaluated. To determine whether melanocytic proliferations arising in a field of LS more closely resembled persistent melanocytic nevi or persistent malignant melanoma, the presence or absence of the following features was assessed on the basis of the criteria originally described by Ackerman et al6 and Kornberg and Ackerman7 and further extended by Park et al8:

1. Sharp circumscription of epidermal melanocytes (ie, do individual melanocytes extend beyond the lateral confines of the dermal fibrosis or sclerosis?)
2. Pagetoid scatter (melanocytes above the basal keratinocyte layer)
3. Melanocytic nests within the fibrosis or sclerosis
4. Confluent melanocytic nests (large melanocytic nests running parallel with the epidermis)
5. Lentiginous melanocytic hyperplasia
6. Trizonal pattern: pagetoid scatter and or confluent nests melanocytes (melanoma in situ pattern) separated by fibrosis or sclerosis from a residual intradermal melanocytic nevus
7. Dermal melanocytic mitotic figures
8. Presence of a lymphocytic host response

If mitotic figures were identified, the number of mitotic figures per high-power field was counted. For cases exhibiting a lymphocytic host response, the lymphocytic infiltrate was further classified as infiltrative (dense infiltrates of lymphocytes surrounding and permeating melanocytic nests) or not (Table 2).

As the melanocytes in LS melanocytic nevi, persistent melanocytic nevi, and persistent malignant melanoma are conspicuous, the nuclear cell diameter of both intraepidermal and dermal melanocytes were measured with a micrometer at ×400 magnification (each unit equals 2.5 µm) to determine whether cell or nuclear size differed among the 4 diagnostic categories. Five representative cells of the epidermal and dermal compartments in each case were measured, from which a mean value was generated. Nuclear-to-cell diameter ratio was calculated with the use of these mean values (Table 2).

HISTOCHEMISTRY AND IMMUNOHISTOCHEMISTRY

Fontana-Masson staining for melanin was performed. Keratinocyte and intraepidermal and dermal melanocyte melanization was histologically assessed in comparison with normal skin as either hypermelanotic, melanotic, hypomelanotic, or amelanotic.

Immunohistochemistry was performed with an automated diaminobenzidine immunohistochemistry system (Ventana ES; Ventana Medical Systems, Inc, Tucson, Ariz) with antibodies against HMB-45 (PMEL17/gp100) (prediluted, Ventana Medical Systems, Inc), and Ki-67 (prediluted, Ventana Medical Systems, Inc). The number of melanocytes labeled with these antibodies per 100 melanocytes was counted to derive the labeling index in both the epidermal and dermal compartments (Table 2).

STATISTICAL ANALYSIS

Statistical analysis was performed with the STATA software package (Stata Corp, College Station, Tex). Differences between groups were tested by the χ² test for dichotomous variables, t test for continuous variables, and analysis of variance (means) for continuous variables across categories. Logistic regression methods were used for categorical analysis. Differences were considered significant when P<.05.

(region after biopsy or excision demonstrated the ivory-white color of LS in the skin surrounding the biopsy site. All of these patients had their melanocytic proliferations completely excised, some with wide margins. No local recurrence, regional lymph node spread, or systemic spread has been reported to date, with a mean disease-free time of 29 months (range, 4-60 months).

By age, patients with melanocytic proliferations arising in LS were significantly younger than those with persistent malignant melanoma (t test, P=.01), and by size, these macules were significantly larger than those of persistent melanocytic nevi (t test, P=.01).
Persistent Melanocytic Nevi

The patients with persistent melanocytic nevi included 8 females and 5 males with a mean age of 36 years (range, 15-75 years). They all had variable dotlike or linear, streak-like macules ranging in size from 1 to 5 mm (mean, 3 mm) arising in the scar of a previously excised compound or predominantly intradermal melanocytic nevus (Figure 1). These persistent nevi recurred within the scar in a mean time of 6 months (range, 1-18 months). They were located on the trunk (6 cases), head and neck (2 cases), pubis and perineum (2 cases), and extremities (3 cases).

Persistent Malignant Melanoma

The 7 patients with persistent melanoma were 2 women and 5 men with a mean age of 66 years (range, 55-78 years). Their malignant melanomas recurred within the surgical scar in a mean time of 40 months (range, 24-60 months) and presented as irregular-bordered brown to black macules or papules with a mean diameter of 7 mm (range, 2-15 mm). These persistent malignant melanomas were located on the chest or shoulder (3 cases), arm (2 cases), and face and calf (1 case each). Compared with persistent melanocytic nevi, persistent malignant melanoma recurred significantly later after primary excision (40 vs 6 months; t test, P = .004).

Ordinary Compound Melanocytic Nevi

The patients with melanocytic nevi were 3 females and 6 males with a mean age of 32 years (range, 15-42 years). Their nevi ranged in size from 2 to 8 mm (mean, 5 mm); the nevi were located on the trunk (6 cases) and the neck, pubis, and cheek (2 cases each). Each nevus was excised to exclude the diagnosis of melanoma or to confirm the clinical impression of dysplastic melanocytic nevus because of their irregular borders and variegated coloration from light brown to dark brown.

HISTOLOGIC FEATURES

Melanocytic proliferations arising in LS were interpreted as junctional melanocytic nevi (5 cases), com-
pound melanocytic nevi (3 cases), intradermal melanocytic nevi (2 cases), or malignant melanoma (1 case). Except for the case of malignant melanoma, all of the LS melanocytic nevi were superimposed on the pathognomonic dermal sclerosis of LS, and those with junctional nests all showed well-circumscribed lateral margins. In these cases, LS extensively involved the surrounding skin.

For cases of LS melanocytic nevi with a dermal melanocytic component, superficial and middermal melanocytic nests were entrapped in the sclerosis. These latter melanocytes were larger than the uninvolved deeper dermal, “residual” melanocytes in melanocytic nevi and exhibited abundant dusty gray cytoplasm and vesicular nuclei similar to melanocytes within the epidermis overlying the sclerosis of LS. All of the LS melanocytic nevi had sparse to dense lymphocytic infiltrates underlying the dermal sclerosis, and in more than half of the cases these lymphocytic infiltrates surrounded and disrupted dermal and junctional melanocytic nests (Figure 2).

In the 1 case of malignant melanoma, the characteristic histologic changes of LS were found at the periphery of the malignant melanoma, neither immediately adjacent to nor underlying it, as found for LS melanocytic nevi. This lesion was histologically diagnosed as a nodular malignant melanoma. Its characteristics consisted of focal pagetoid spread overlying large, sheetlike dermal nests of markedly pleomorphic melanocytes that exhibited numerous mitotic figures (8 per 10 high-power fields) and had a tumor thickness of 2.7 mm, Clark level 4. No changes of regression and a sparse tumor infiltrating lymphocytic host response were evident.

### Table 2. Comparison of Melanocytic Proliferations Arising in LS With Those in Compound Melanocytic Nevi, Persistent (Recurrent) Melanocytic Nevi, and Persistent (Locally Recurrent) Malignant Melanoma

<table>
<thead>
<tr>
<th>Feature</th>
<th>LS Nevi† (n = 10)</th>
<th>Persistent Nevi (n = 13)</th>
<th>Persistent Melanoma‡ (n = 7)</th>
<th>Compound Nevi (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical size, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>6</td>
<td>3</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Range</td>
<td>2-18</td>
<td>1-5</td>
<td>2-15</td>
<td>2-8</td>
</tr>
<tr>
<td>Histologic characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral extension, No. (%)</td>
<td>0</td>
<td>0</td>
<td>5 (71)</td>
<td>NA</td>
</tr>
<tr>
<td>Pagetoid scatter, No. (%)</td>
<td>3 (33)</td>
<td>2 (15)</td>
<td>6 (86)</td>
<td>NA</td>
</tr>
<tr>
<td>Melanocytes within fibrosis/sclerosis, No. (%)</td>
<td>8 (87)</td>
<td>5 (38)</td>
<td>6 (86)</td>
<td>NA</td>
</tr>
<tr>
<td>Confluent junctional nests, No. (%)</td>
<td>7 (78)</td>
<td>5 (38)</td>
<td>6 (86)</td>
<td>NA</td>
</tr>
<tr>
<td>Lentiginous melanocytic hyperplasia, No. (%)</td>
<td>6 (67)</td>
<td>12 (92)</td>
<td>5 (71)</td>
<td>NA</td>
</tr>
<tr>
<td>Dermal (residual) melanocytic nevus, No. (%)</td>
<td>5 (55)</td>
<td>5 (38)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Trizonal pattern, No. (%)</td>
<td>2 (22)</td>
<td>3 (23)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Mitotic figures (dermal)/HPF</td>
<td>0</td>
<td>0</td>
<td>1 (0-2)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytic host response, No. (%)</td>
<td>9 (100)</td>
<td>12 (92)</td>
<td>5 (71)</td>
<td>0</td>
</tr>
<tr>
<td>Infiltrative host response, No. (%)</td>
<td>5 (55)</td>
<td>3 (23)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Immunolabeling, mean (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HMB-45 LI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermal melanocytes</td>
<td>80 (60-100)</td>
<td>72 (10-100)</td>
<td>82 (30-100)</td>
<td>23 (2-55)</td>
</tr>
<tr>
<td>Dermal melanocytes</td>
<td>20 (0-80)</td>
<td>18 (0-50)</td>
<td>34 (0-75)</td>
<td>5 (0-30)</td>
</tr>
<tr>
<td>Ki-67 LI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermal melanocytes</td>
<td>3 (1-6)</td>
<td>3 (0-12)</td>
<td>14 (2-30)</td>
<td>2 (0-6)</td>
</tr>
<tr>
<td>Dermal melanocytes</td>
<td>2 (0-10)</td>
<td>3 (0-10)</td>
<td>15 (7-24)</td>
<td>1 (0-3)</td>
</tr>
<tr>
<td>Cell and nuclear size, mean (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermal nuclear diameter, units§</td>
<td>3 (2-5)</td>
<td>3 (2-5)</td>
<td>6 (5-8)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>Epidermal melanocyte diameter, units§</td>
<td>6 (4-8)</td>
<td>6 (5-8)</td>
<td>10 (7-15)</td>
<td>6 (4-7)</td>
</tr>
<tr>
<td>Epidermal N/C ratio</td>
<td>0.54</td>
<td>0.56</td>
<td>0.58</td>
<td>0.58</td>
</tr>
<tr>
<td>Dermal nuclear diameter, units§</td>
<td>4 (3-7)</td>
<td>3 (3-4)</td>
<td>5 (4-6)</td>
<td>3 (2-4)</td>
</tr>
<tr>
<td>Dermal melanocyte diameter, units§</td>
<td>6 (5-10)</td>
<td>5 (5-6)</td>
<td>8 (5-10)</td>
<td>5 (3-6)</td>
</tr>
<tr>
<td>Dermal N/C ratio</td>
<td>0.71</td>
<td>0.64</td>
<td>0.70</td>
<td>0.63</td>
</tr>
</tbody>
</table>

*LS indicates lichen sclerosus; NA, not applicable because of the absence of dermal fibrosis or sclerosis; HPF, high-power field; LI, labeling index (number of positive cells per number of melanocytes counted); and N/C, nuclear–cell size ratio.
†Case 10 of the malignant melanomas is not included in this analysis because LS was found at its periphery, whereas in all other cases the melanocytic proliferation was superimposed on the histologic features of LS.
‡Data derived from 4 persistent in situ melanomas and 3 invasive melanomas (dermal component with an in situ component in 2 cases).
§Each unit is 2.5 µm.

The vulvar malignant melanoma that was surrounded but not directly involved by the LS was excluded from this analysis. The LS melanocytic nevi had many features in common with persistent melanocytic nevi, such as confluent junctional nests, pagetoid melanocyte spread, nests of melanocytes trapped within dermal sclerosis, lentiginous melanocytic hyperplasia, peritumoral lymphocytic infiltrates, residual dermal melanocytic nevus, and the presence of a trizonal pattern (Table 2). Most of these histologic features were also present in persistent malignant melanoma. The presence of lateral extension of intradermal melanocytes beyond the dermal fibrosis, the absence of a residual intradermal melanocytic nevus, absence of a trizonal pattern, and/or presence of dermal mi-
totic figures differentiated malignant melanoma from both LS melanocytic nevi and persistent melanocytic nevi (logistic regression, univariate and multivariate analysis, \( P < .001 \)). In addition, the finding of pagetoid scatter, although present in all 3 clinical settings, occurred significantly more often in persistent malignant melanoma and was predictive of malignant melanoma (\( \chi^2 \) and logistic regression tests, \( P \leq .01 \)). Moreover, confluent junc-
tional nests were significantly more common in both per-
sistent malignant melanoma and LS melanocytic nevi than in persistent melanocytic nevi (\( \chi^2 \) test, \( P = .03 \)).

Melanin Content

In regions of the epidermis overlying scars without an intraepidermal melanocytic proliferation (neviod or ma-
lignant melanocytes), keratinocytes were hypomela-
nized as compared with those of the adjacent normal epi-
dermis. Dendritic, “nonproliferating” melanocytes in these regions showed normal to diminished melanin content. In stark contrast, both melanocytes and contiguous ke-
ratinocytes in regions of melanocytic proliferations over-
lying dermal fibrosis and sclerosis exhibited hypermelan-
zation compared with normal adjacent epidermis. In addition, numerous melanin granules were present throughout all layers of the affected epidermis (spino-
uous, granular, and stratum corneum) compared with nor-
mal epidermis, where melanin was concentrated in the

basal layer overlying the nucleus. Dermal melanocytes entrapped within the fibrosis or sclerosis also showed hy-
permelanization (Figure 3). The degree and extent of melanin content were similar between LS nevi and per-
sistent nevi, whereas these findings were more variable in persistent malignant melanoma, ranging from focal melanization of melanocytes to intense and diffuse hy-
permelanization of both malignant melanocytes and ad-
jacent keratinocytes. In ordinary melanocytic nevi, scat-
tered nested or solitary melanocytes and adjacent keratinocytes and scattered superficial dermal melano-
cytes showed hypermelanization.

Melanocyte Cell and Nuclear Size

Both qualitatively and quantitatively, melanocytes in LS melano-
cytic nevi and persistent melanocytic nevi most closely resembled one another, were slightly larger than those in ordinary nevi, and were significantly smaller than those in persistent malignant melanoma (analysis of vari-
ance, \( P = .01 \)) (Table 2). In general, nevoid melanocytes of LS nevi and persistent nevi showed “pagetoid” cyto-
logic findings in the form of enlarged cells with abun-
dant pale to dusty gray cytoplasm and oval, vesicular (reactive) nucleus with prominent nucleoli. Similar-
appearing melanocytes could also be found in the junc-
tional nests of compound melanocytic nevi, but these cells were not as prevalent. Dermal nevoid melanocytes not
affected by dermal fibrosis or sclerosis (residual melanocytic nevi) were similar qualitatively and quantitatively to ordinary melanocytic nevi. Although the melanocytes in persistent malignant melanoma were significantly larger than those in the other 3 categories, the ratio of cell diameter to nuclear diameter did not significantly differ between any of the 4 categories.

**IMMUNOHISTOCHEMICAL FINDINGS**

**HMB-45 Expression**

Intense and diffuse labeling of melanocytes by HMB-45 was found in LS melanocytic nevi and persistent melanocytic nevi, particularly for the epidermal component compared with superficial dermal melanocytes entrapped within sclerosis or fibrosis (Table 2). In addition, melanocytes entrapped in fibrosis or sclerosis showed more intense and extensive HMB-45 labeling than did superficial dermal melanocytes of ordinary melanocytic nevi. Morphometric analysis of the frequency and intensity of immunostaining showed that LS melanocyte nevi and persistent melanocytic nevi had significantly larger labeling indexes than those of compound melanocytic nevi (analysis of variance, $P < .001$). Although both LS nevi and persistent nevi had a larger fraction of dermal melanocytes marking with HMB-45, their staining was not significantly different from that of compound melanocytic nevi. Persistent malignant melanoma’s HMB-45 labeling index, both epidermal and dermal compartments, was not significantly different from that of LS melanocytic nevi or persistent melanocytic nevi. However, within the dermis, HMB-45 staining was generally greater and could be found in the deep dermis—a characteristic not found in persistent melanocytic nevi, LS melanocytic nevi, or ordinary melanocytic nevi.

**Ki-67 Antigen Expression**

Ki-67 (MIB-1) is a cell cycle antigen expressed throughout all active stages of the cell cycle (G1, S, G2, and M); thus, the number of cells expressing this antigen would represent the number of proliferating cells. The highest Ki-67 labeling index was found in persistent malignant melanoma, being significantly greater than that in LS melanocytic nevi, persistent melanocytic nevi and ordinary melanocytic nevi for both epidermal and dermal melanocytes (analysis of variance, $P < .001$) (Table 2). There was no significant difference between the latter 3 entities in Ki-67 labeling.

**COMMENT**

Lichen sclerosus is a chronic fibroinflammatory dermatosis of unknown etiology that can produce substantial discomfort and morbidity. Although LS most com-
Lichen sclerosus most commonly occurs in women, it is also found in men and children. Any skin site may be affected; however, LS is most prevalent in the anogenital area, where it sometimes causes intractable itching, soreness, and, in some patients, destructive scarring and/or squamous cell carcinoma. Lichen sclerosus can occur without symptoms, which may, in part, be responsible for its uncertain prevalence. In children, LS, predominantly vulvar and often unrecognized, can be interpreted as a sign of sexual abuse because of purpura and erosions, or can lead to dysuria and pain on defecation. Rarely, childhood LS has been reported concomitant with vulvar malignant melanoma. Clinically, LS is denoted by its white, nonpigmented or vitiligolike appearance. Clinical pigmentation caused by a melanocytic proliferation as a presenting sign of vulvar LS has not been reported in childhood LS but this pattern of presentation appears to affect about 1% of women with LS. The clinicopathologic findings of the LS junctional and compound melanocytic nevi occurring in young females presented herein are strikingly similar to those reported for vulvar malignant melanoma associated with LS (Table 1). In contrast, our one case of vulvar malignant melanoma associated with LS at its periphery has more in common with conventional vulvar malignant melanoma.

Both childhood and vulvar malignant melanoma are rare, with incidences of 0.8 to 8 per million and 1 per million, respectively. Established risk factors for childhood malignant melanoma are giant and small congenital melanocytic nevi, xeroderma pigmentosum, atypical or dysplastic mole syndrome, eruptive melanocytic nevi associated with immunosuppression, preexisting common acquired melanocytic nevi, and cutaneous sensitivity to the effects of sun exposure (ie, freckling). Neither LS nor a vulvar location has been described in these reported series of childhood malignant melanoma. In comparison, vulvar malignant melanoma is thought to be biologically different from cutaneous malignant melanoma, and, on the basis of incidence and relative surface areas affected, malignant melanoma may in fact show a predisposition for the vulva compared with nongenital skin. Furthermore, vulvar malignant melanoma is a disease of older women (median age, 66 years at diagnosis) and has a much poorer prognosis than cutaneous malignant melanoma (47% vs 80% 5-year survival). In a study of 219 Swedish women, only 18 were younger than 44 years and none was younger than 15 years. Nonetheless, 6 girls younger than 16 years have been described with vulvar malignant melanoma in several large series. With respect to LS and vulvar malignant melano-
Lichen Sclerosus Melanocytic Nevi, Persistent (Recurred) Melanocytic Nevi Pathologic Features

<table>
<thead>
<tr>
<th>Lichen Sclerosus Melanocytic Nevi</th>
<th>Persistent (Recurred) Melanocytic Nevi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reappearance in &lt; 2 y (persistent nevi)</td>
<td>Reappearance in ≥ 2 y</td>
</tr>
<tr>
<td>Sharply circumscribed borders</td>
<td>Extension of melanocytes past fibrosis</td>
</tr>
<tr>
<td>Minimal pagetoid scatter, if present</td>
<td>Extensive pagetoid scatter</td>
</tr>
<tr>
<td>Trizonal pattern (melanoma in situ pattern/scar/dermal nevus)</td>
<td>Absent trizonal pattern</td>
</tr>
<tr>
<td>Concomitant dermal melanocytic nevus</td>
<td>No associated dermal melanocytic nevus</td>
</tr>
<tr>
<td>No dermal mitotic figures</td>
<td>Dermal mitotic figures</td>
</tr>
<tr>
<td>HMB-45 expression confined to dermal melanocytes within sclerosis</td>
<td>Deep dermal HMB-45 expression</td>
</tr>
<tr>
<td>Ki-67 index &lt; 10%</td>
<td>Ki-67 labeling index ≥ 10%</td>
</tr>
</tbody>
</table>

noma, LS has not been histologically documented in any series of vulvar malignant melanoma, although the possibility of its presence exists on the basis of clinical descriptions of leukoplakia or ivory-white skin concurrent with malignant melanoma. Thus, the absence of significant overlap between childhood and vulvar variants of malignant melanoma would indicate that their co-incidence is improbable.

Just as persistent melanocytic nevus can mimic malignant melanoma, melanocytic nevus of genital skin can present difficulties in histologic interpretation, leading to the misdiagnosis of malignant melanoma. These “atypical” genital melanocytic nevus occur most commonly on the vulva (labia minora and clitoral region) of young women (median age, 25 years) and contain an underlying stroma that is different from that of dysplastic melanocytic nevi and malignant melanoma. The histologic features that overlap with malignant melanoma are (1) their wide lateral extent, (2) lack of uniformity in sizes and shapes of melanocytes within the epidermis, (3) confluence of some junctional melanocytes, and (4) presence of melanocytes, both singly and in nests within adnexal structures. The discriminating features that allow for differentiation from malignant melanoma are the presence of (1) sharp demarcation of epidermal melanocytic component, (2) symmetry of the lesion, (3) absence of pagetoid spread, and (4) maturation of the melanocytes, with progressive descent into the dermis. With the exception of pagetoid spread and symmetry, vulvar LS melanocytic nevus share the same clinical profile and the same histologic features of sharp circumscription, confluent junctional nests, and dermal melanocyte maturation with “atypical” genital melanocytic nevi.

Keratinocytes and melanocytes overlying scars and LS exhibit an activated phenotype denoted by increased proliferation and inverse expression of envelope proteins (eg, involucrin) by keratinocytes and HMB-45 expression and increased proliferation of melanocytes. The similarity of LS melanocytic nevi to persistent melanocytic nevi is not unexpected. Although persistent melanocytic nevus also showed many of the same histologic and immunophenotypic features, the presence or absence of crucial histologic features and the higher variability and greater degree of immunophenotypic changes can distinguish malignant melanoma from both LS melanocytic nevi and persistent melanocytic nevus (Table 3). Histologically, sharp demarcation of junctional melanocytic hyperplasia that is limited to the area above the dermal fibrosis-sclerosis and the presence of a residual melanocytic nevus were not features of persistent melanoma. Variable and deep dermal HMB-45 expression and significantly greater growth fraction in the form of mitotic figures and Ki-67 antigen expression found in this study separated persistent malignant melanoma from LS melanocytic nevus and persistent melanocytic nevus and more closely resembled that described for conventional malignant melanoma.

The finding of residual or uninvolved dermal melanocytic nevus in LS melanocytic nevus indicates that melanocytic nevus may precede the development of LS. However, it is possible that LS induces the formation of a melanocytic nevus. Clinical pigmentation caused by melanocytic hyperplasia affects approximately 8% to 30% of surgical scars and may be related to production of cytokines, growth factors, neuromodulators, and chemical composition of the extracellular matrix by the pathologically altered dermis, or disruption of the basement membrane zone. Underscoring this mesenchyme-melanocyte interaction are investigations showing that extracellular matrix proteins modify melanocyte morphologic characteristics, proliferation, and melanogenesis. Thus, the marked black clinical pigmentation and enlarged, melanogenic melanocytes found in both LS melanocytic nevi and persistent melanocytic nevi would be induced by secretronically active mesenchymal cells of the dermis surrounding the nevoid melanocytes. Alternatively, formation of melanocytic nevus could be induced de novo from predisposed melanocytes and activated mesenchyme and pathologically changed extracellular matrix of LS.

It is tempting to suggest that LS could act as a cofactor in the development of vulvar malignant melanoma through the analogy with the well-documented phenomenon of chronic inflammation and scarring giving rise to cancer (eg, squamous cell carcinoma secondary to long-standing scars). For example, vulvar LS has a cumulative risk of 14.8% for the development of squamous cell carcinoma, and the incidence of vulvar squamous cell carcinoma increases as a function of age from 1.8 to 20 per 100 000 by age 80 years. In the etiology of squamous cell carcinoma, LS would act as both an initiator and a promoter of carcinogenesis via its inflammatory infiltrate rich in macrophages producing free radicals.
radicals and the induced proliferative activity of affected keratinocytes, respectively. Since UV radiation, the only proved environmental “melanocytic carcinogén,” does not access the vulva or vaginal mucosa, we propose that local stressors and defective mechanisms of reestablishing local tissue homeostasis would initiate and/or facilitate vulvar melanoma development. Lichen sclerosus is an example of such a condition, eg, it would generate a pro-oxidative environment, increase the risk of mutation, and, by changing the extracellular matrix composition and repertoire of cytokines and growth factors produced, facilitate clonal expansion of damaged melanocytes. Moreover, dense subepidermal fibrosis-sclerosis would provide a relative shield against T-cytotoxic T lymphocytes, allowing for expansion of melanocytes with an abnormal phenotype. As underreporting and lack of recognition of vulvar dermatoses in the skin adjacent to squamous cell carcinoma have been well documented, we expect that a similar practice is responsible for the scarcity or absence of reports of LS adjacent to vulvar malignant melanoma. The lack of thorough analysis of the skin associated with vulvar malignant melanoma is highlighted by the unknown role of preexisting vulvar melanocytic nevi in its formation. Although many series of cases of vulvar malignant melanoma report a history of a preexisting melanocytic nevus, few series histologically document preexisting vulvar melanocytic nevi, which has a frequency of less than 1% of all vulvar malignant melanomas. To test the above hypothesis, future clinical and pathological reporting of vulvar malignant melanoma should attempt to more carefully analyze the adjacent skin to document the prevalence of coexisting inflammatory conditions (LS), melanocytic precursors, or genital melanosis. As the development of cancer involves tumor-stroma interactions, the absence of sclerosis underlying or adjacent to vulvar malignant melanomas (or squamous cell carcinomas) would reflect the phenomenon of tumor progression characterized by changes in neoplastic cells proceeding in concert with alterations in the extracellular matrix.

CONCLUSIONS

We conclude that melanocytic nevi can be found superimposed on LS and that malignant melanomas can arise in the background of LS. The high frequency of genital involvement and restriction to females is likely a reflection of the overwhelming predilection of LS for female genitalia. Melanocytic nevi in LS, both clinically and histologically, can mimic malignant melanoma and, thus, are akin to persistent melanocytic nevi or so-called pseudomelanoma. The overlapping morphologic features with malignant melanoma are likely caused by the stromal alterations that may induce a change in melanocyte phenotype. Nonetheless, key histologic features can confidently separate LS melanocytic nevi from malignant melanomas. Malignant melanomas exhibit poorly circumscribed junctional melanocytes that extend past dermal changes of fibrosis-sclerosis, dermal mitotic figures, and deep HMB-45 expression. Malignant melanomas also lack the trizonal pattern and/or a dermal melanocytic nevi underlying the sclerosis found in LS melanocytic nevi. Although the possibility of an aggressive course cannot be entirely excluded without longer follow-up, the striking similarity to persistent melanocytic nevi and the absence of recurrence in this series underscore the benign nature of LS melanocytic nevi. Finally, regardless of a coincidental or causal relationship, LS would be predicted to be a prevalent finding in the skin and mucosa surrounding vulvar malignant melanomas, considering the high incidence of these 2 conditions in older women and the well-documented underreporting of LS adjacent to vulvar squamous cell carcinomas.

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