Lentigo Maligna
Melanoma In Situ on Chronically Sun-Damaged Skin

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Objective.—To focus on lentigo maligna, the preinvasive/in situ form of melanoma located on chronically sun-damaged skin.

Data Sources.—Review of the literature and the authors’ personal experiences.

Conclusions.—A better understanding of the earliest stage of melanoma progression, including the contribution of chronic exposure to ultraviolet radiation, may lead to improved classification schemes that direct more effective targeted or personalized therapies for patients.

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Primary cutaneous malignant melanoma often is classified by histologic subtype. The most common of these subtypes include superficial spreading, nodular, lentigo maligna melanoma, and acral lentiginous. The concept of an earlier, preinvasive stage of melanoma in which neoplastic cells are confined to the epidermis was advanced by studies of tumor progression in other organs and by a better understanding of the biology of normal intraepidermal melanocytes.

In sun-protected adult human skin, intraepidermal melanocytes remain in a quiescent, growth-arrested (G0) state within the basal layer, proliferating approximately once a year. Chronic exposure to ultraviolet (UV) radiation, however, induces melanocytes first to increase production of melanin, and then to enter the cell cycle, proliferating more frequently. Exposure to UV radiation also may induce DNA damage and increase the likelihood of mutations that alter regulation of the normal cell cycle.

The earliest histologically recognizable stage of malignant melanoma is characterized by an increased number of intraepidermal melanocytes displaying architectural disarray and cytologic atypia, but without the capability of dermal invasion (ie, melanoma in situ). Melanoma in situ may occur de novo or may arise within the intraepidermal component of a preexistent melanocytic nevus. Several factors have been linked to melanomagenesis, including a familial history of melanoma, a personal history of sunburns (especially during adolescence), or a personal history of chronic sun exposure. Although genetic instability and dysregulated proliferation of melanocytes are hallmarks of all malignant melanomas, this review will focus on the subtype of preinvasive, intraepidermal melanoma associated specifically with chronic exposure to UV radiation (lentigo maligna).

CLINICAL FEATURES OF LENTIGO MALIGNA

Most patients with lentigo maligna present with a slowly enlarging pigmented macule or patch, usually on the head or neck, although any anatomic site with a history of chronic exposure to UV radiation may be involved. Individual lesions are characterized by asymmetry, an irregular peripheral border, variegated color, enlarging diameter, and change in appearance over time. Areas of partial regression within the lesion are not uncommon. The appellation lentigo maligna has been used because of the lesion’s clinical resemblance to an actinic/solar lentigo and/or because of some authors’ unwillingness to label these lesions as a malignancy per se. In fact, lentigo maligna also has been called Hutchinson melanotic freckle and melanosis circumscripita precancerosa Dubreuilh.

Another fortunately rare clinical variant of lentigo maligna presents as an enlarging, hypopigmented or erythematous, scaly patch resembling eczema, Bowen disease (squamous cell carcinoma in situ), or a superficial basal cell carcinoma. Such cases of amelanotic melanoma in situ lack classical morphologic features and may thus easily elude clinical diagnosis. Amelanotic lentigo maligna may develop spontaneously or may arise from a previously treated pigmented lentigo maligna.

Whether clinically hyperpigmented or amelanotic, some authors consider lentigo maligna to be an earlier...
atypical melanocytic proliferation (hyperplasia) on chronically sun-damaged skin histologically distinct from melanoma in situ, lentigo maligna type, the preinvasive form of lentigo maligna melanoma. Others have proposed that the term lentigo maligna be abandoned altogether for the broader term melanoma in situ, with less emphasis placed on chronic sun exposure. Regardless of nomenclature, most dermatologists and dermatopathologists recognize a preinvasive form of melanoma on chronically sun-damaged skin, with the understanding that tumor progression for any given patient may evolve over a protracted course of many years or not at all.

**HISTOLOGIC FEATURES OF LENTIGO MALIGNA**

Most melanomas arising on chronically sun-damaged skin have a characteristic histologic appearance, whereas those arising on intermittently sun-exposed skin or within a preexisting melanocytic nevus have more variable features. By definition, lentigo maligna occurs on chronically sun-damaged skin. As such, histologic features related to chronic sun damage such as epidermal atrophy, increased pigmentation in basal keratinocytes, and prominent solar elastosis are present (Figure 1, A and B). The melanocytes are increased in number, and as in solar lentigines, often are disposed as single cells along the basal layer. Nests of melanocytes may be present, but are unevenly distributed across the lesion. Multinucleated (starburst) melanocytes also may be present, but this feature is not specific for lentigo maligna. A few melanocytes may permeate superficial epidermal layers; involvement of cutaneous adnexal structures is common. Nuclear atypia is variable and may be subtle. In this latter respect, aberrations of architecture may be much more pronounced than the degree of cytologic atypia. Importantly, smaller atypical melanocytes of lentigo maligna may be partially obscured by surrounding enlarged pigmented basal keratinocytes. Unfortunately, the presence of an early, pigmented actinic keratosis or of a pigmented macular seborrheic keratosis on chronically sun-damaged skin does not preclude concurrent lentigo maligna. In such cases, rete ridges may be elongated rather than attenuated (Figure 1, C).

**IMMUNOHISTOCHEMISTRY AS A DIAGNOSTIC AID**

Distinguishing lentigo maligna from a background of increased melanocytes on chronically sun-damaged skin in a small biopsy specimen remains one of the most difficult diagnostic challenges for dermatopathologists. A similar challenge may occur when evaluating peripheral margins of a melanoma reexcision in which melanocytes are increased in number within the epidermis overlying a prior biopsy scar. This challenge is especially problematic when faced with the task of interpreting en face frozen section margins of lentigo maligna. To these ends, several authors have advocated the use of immunohistochemistry to better enumerate intraepidermal melanocytes. Several markers of lentigo maligna differentiation have been used for these studies, each with its own set of advantages and limitations. These techniques are particularly useful for identifying amelanotic lentigo maligna or intraepidermal melanocytes that are partially obscured by surrounding pigmented basal keratinocytes (Figure 2, A through D). In the authors’ opinion, careful interpretation of immunolabeling patterns for a combination of markers such as melanosomal glycoproteins gp100 and Melan-A/MART-1 may mitigate the lack of sensitivity and specificity previously documented for individual antibodies.
The Classification of Melanoma Based on Genetic Aberrations

Although it is convenient for dermatopathologists to classify melanomas by their histologic appearance, advances in our understanding of melanoma biology suggest that these lesions might be better grouped by their biologic behavior or by their likelihood of response to a particular therapy.

One of the earliest major advances in our understanding of melanoma biology came from the identification of the genetic locus linked to the familial melanoma syndrome in which homozygous deletion or loss of heterozygosity at 9p21 results in loss or diminution of expression of the tumor suppressor p16^{INK4a}.\(^ \text{13,38,39} \)

Subsequently, other groups\(^ \text{40–42} \) identified activating mutations within the mitogen-activated protein kinase (MAPK) signaling pathway in most sporadic melanomas. This discovery has driven the development of several MAPK pathway inhibitors currently being tested in clinical trials for advanced stage disease.

More recently, Bastian and colleagues\(^ \text{43} \) and Curtin and colleagues\(^ \text{44} \) advanced a classification scheme for melanoma, based on commonly occurring genetic aberrations.

Melanomas classified in this way largely harbor nonrandom amplifications or deletions of chromosomal regions that correlate with specific anatomic sites (melanomas on acral skin and mucosal melanomas) or with the amount of sun exposure (chronic, intermittent, or little). It is tempting to speculate that at least some of the genetic aberrations common to invasive melanomas arising on chronically sun-damaged skin would be shared by lentigo maligna. However, most of the data from these studies were derived from primary invasive tumors. Of interest, cytogenetic abnormalities have been documented both in cultured cell lines derived from lentigo maligna and by fluorescence in situ hybridization performed on biopsies of lentigo maligna.\(^ \text{45,46} \)

Melanomas also may differ in their protein signaling pathways as a function of the degree of chronic sun exposure; for example, the transcription factor PAX3 is more commonly expressed in melanomas with low or no evidence of UV damage.\(^ \text{47} \) Classification of melanoma based solely upon aberrations of protein signaling, however, is confounded by known alterations of protein trafficking and by epigenetic mechanisms controlling protein expression.\(^ \text{48–50} \) Clearly, a classification scheme

Figure 2. Amelanotic lentigo maligna clinically presenting as a patch of “eczema.” A and B, Note the lack of melanin pigment. Melanocytes are partially obscured by the surrounding enlarged basal keratinocytes. C, Immunohistochemical labeling for gp100 (using HMB-45). D, Immunohistochemical labeling for Melan-A/MART-1 (hematoxylin-eosin, original magnifications ×86 [A] and ×172 [B]; original magnifications ×172 [C and D]).
for melanoma based on only one aspect of tumor biology is insufficient.

**DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS**

Surgical excision remains the most common therapy for patients with lentigo maligna. A variety of other therapies including radiotherapy, laser ablation, and use of topical immune system modulators have been used with variable success for patients with large lesions or who are not otherwise candidates for surgery.25,26 By developing a more precise classification of melanoma based on a combination of clinical information, histologic appearance, genotype, and alterations in cellular signaling pathways, it may be possible one day to construct a road map for therapeutic interventions tailored to individual patients.

**References**


