

Early diagnosis of malignant melanoma: Proposal of a working formulation for the management of cutaneous pigmented lesions from the Melanoma Cooperative Group*

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Abstract. Epiluminescence microscopy (ELM) strongly improves the separation of different types of cutaneous pigmented lesions (CPL) and facilitates the early diagnosis of cutaneous melanoma (CM). ELM alone is not 100% accurate in routine diagnosis, and should not be considered the only criterion in the diagnosis of high-risk skin lesions. We have however, demonstrated close agreement between ELM classification criteria and histology in 2,731 cutaneous lesions. In the past five years, our Melanoma Cooperative Group has evaluated 61,000 skin lesions from 30,000 individuals and identified 478 cutaneous melanomas. Most newly diagnosed patients had very early stage melanoma [299 (62%) were Stage I (203 Stage IA and 96 Stage IB), by the American Joint Committee on Cancer (AJCC) criteria]. We have

compared data from the patient histories and clinical evaluations with ELM-based morphological patterns to better characterize skin lesions and minimize interpretative problems. From these comparisons, we propose new guidelines for the management of CPL to provide a standard diagnostic and therapeutic approaches and to foster the early identification of lesions at risk for malignant transformation.

Introduction

Epiluminescence microscopy (ELM) has been demonstrated to be a reliable tool for the differential diagnosis of cutaneous pigmented lesions (CPL) and, the early diagnosis of cutaneous melanoma (CM) (1-9). The incidence of CM has risen significantly over the last 50 years in Caucasian populations. Mortality is related to the micrometer-measured (Breslow) thickness of the lesion, a measure that correlates well with lesional evolution. Early detection followed by complete surgical excision is therefore crucial to reducing mortality from CM.

To improve diagnostic accuracy and further define practical criteria for evaluation of CPL (10-16), we have studied the effectiveness of ELM in the diagnosis of CM in a demanding high patient volume setting. We have demonstrated that early CM, atypical naevi and borderline lesions can be accurately identified by ELM (17,18). Our ELM-based results agree well with histology and show very high sensitivity and specificity in the diagnosis of CPL (18). However, some 'borderline' lesions (melanocytic lesion without clear benign or malignant features on histology (19) were misinterpreted and thus misclassified. ELM alone is not 100% sensitive for routine diagnosis, and must be integrated with the patient's history and clinical evaluation (17,18).

In 1994, Kenet and Fitzpatrick introduced clinically useful risk-stratification criteria for the classification of CPL, based on pigment networks evaluated by specific ELM-features

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(20). They proposed four basic types of melanocytic lesions with different risks of progression. Starting from this existing classification (used extensively in our previous studies), we have closely compared clinical and histological characteristics with ELM-based morphological patterns to better characterize skin lesions and reduce interpretative problems (17,18). Application of a risk-related classification to 2,731 excised cutaneous lesions, demonstrated excellent agreement between ELM classification criteria and histological findings (17,18,21). From these results and, evaluation of a larger group of CPL, new guideline for clinical interpretation and management CPL have been generated from a close collaboration between ELM practitioners and pathologists at the National Cancer Institute-Melanoma Cooperative Group (NCI-MCG).

Patients and methods

A campaign for the early diagnosis of cutaneous malignant melanoma has been mounted at the National Cancer Institute of Naples. Several physicians undertook extensive screening activity (~6000 visits per year) to classify individual cutaneous pigmented lesions and evaluate their risk of malignant transformation.

From 1996 to 2000, 30,098 individuals [19,102 females and 10,996 males; median age 34 (range 1-93 years)] underwent a total-body skin examination, and 61,123-pigmented lesions were evaluated using a hand-held video microscope imaging system (MS 500B Micro-Scopeman, Moritex), with a zoom lens that allowed x10, x25 and x50 magnification. In the last three years, we have also utilized three Molemax II (Derma Instruments, Vienna) video-dermatoscopes, which we have provided the possibility of web connection and immediate remote clinical consultation (21).

A personal profile was created for each patient. A carefully recorded history included: (a), information on any familial history of melanoma or dysplastic nevus syndrome. The family history for cancer was evaluated by questionnaire and interviews of individuals attending the Clinics of the Melanoma Cooperative Group at the National Tumor Institute of Naples; (b), extent of sun exposure: place of birth and other areas of residence, type of work, sunburn(s) before the age of 15 years, exposure during times of intense solar radiation, holidays spent at the beach, participation in outdoor sports, occupational sun exposure; (c), individual medical status (e.g. pregnancy, depression, anxiety, associated diseases (in particular, those affecting the immune system).

For lesions subjected to surgical treatment, local excision was performed with adequate margins of excision (1-3 cm). For cutaneous melanoma, lymphatic mapping was used to find the sentinel lymph node (the node with the highest probability of metastasis). This procedure limits the number of patients requiring full lymphadenectomy.

Histopathologic examination of the cutaneous tumor was performed using formalin-fixed paraffin-embedded tissue samples and hematoxylin/eosin staining with (in case of suspected CM lesions) immunohistochemistry (IHC) of adjacent sections. For IHC, 4- μ m-thick sections were evaluated using antibodies against HMB-45 and S-100 protein. To evaluate the level of agreement between ELM and histology, Cohen's κ statistic was calculated.

Table I. ELM-based classification of melanocytic lesions.^a

Melanocytic lesions	ELM features
Type 1 (very high risk)	Lesion with a pigment network and any of the classical ELM features specific for melanoma
Type 2 (high risk)	Lesion with a pigment network and subtle new ELM features that may suggest melanoma but often are also seen in atypical nevi
Type 3 (medium risk)	Lesion with a pigment network carrying subtle perturbations that can be detected in atypical naevus as well as in melanocytic hyperplasia
Type 4 (low risk)	Lesion with a benign appearing network
Type 5 (very low risk)	Lesion with a benign appearing network and with a globular pattern or another benign ELM pattern

^aMelanocytic lesions are classified according to risk stratification criteria (17) and the corresponding ELM features are reported.

Results

During recent screening activity at our Melanoma Cooperative Group, 478 new patients with CM were diagnosed [median age 46 years (range 18-78); 287 females and 191 males (F:M ratio 1.5:1)]. Patients were grouped by disease stage, according to the American Joint Committee on Cancer (AJCC) guidelines. Most CM patients (461; 96%) presented with localized disease at diagnosis [203 (42%) stage IA, 96 (20%) stage IB, 121 (25%) stage IIA, and 41 (9%) stage IIB], and 17 with advanced melanoma [14 (3%) stage III with lymph node involvement, and 3 (1%) stage IV with metastatic disease]. Most CM were asymptomatic and were diagnosed using the ELM approach [64 (32%) of the 203 stage IA melanomas were *in situ* lesions].

Comparison of the histological observations and ELM assessments in the excised lesions, gave overall agreement of 89%. In comparison using the Kenet and Fitzpatrick (K&F) risk-stratification criteria, histology-ELM agreement ranged from 85% for high risk lesions to 94% for very high-risk lesions.

From such findings and on the basis of our experience in this field (17,18), we propose an algorithm to improve accuracy of clinical assessment of pigmented lesions.

Step 1: history and clinical evaluation

History. A family history of melanoma or dysplastic nevi indicates the involvement of genetic factors and increased melanoma susceptibility. Sun exposure is the main environmental risk factor for melanoma, though the

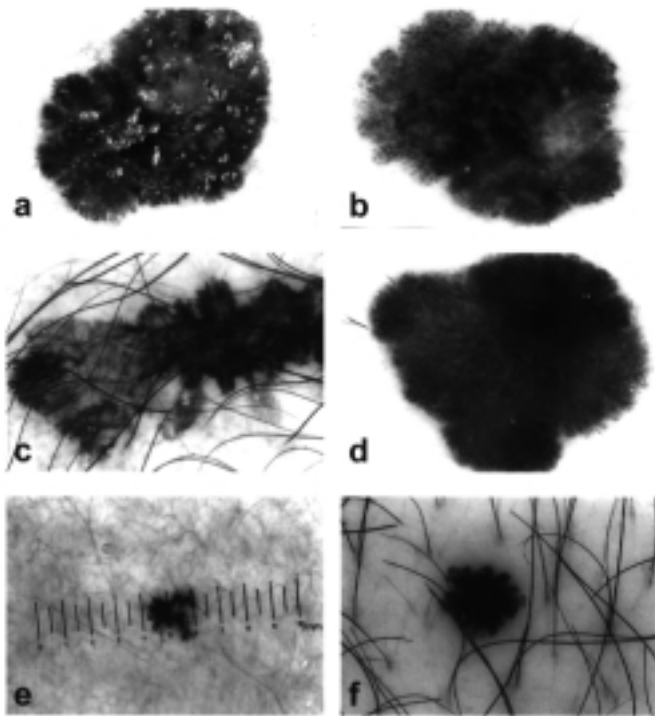


Figure 1. ELM images (by Molemax II apparatus) of type 1 lesions: (a-c), typical ELM images of cutaneous melanoma (CM) with a Breslow thickness of 0.55 and 0.3 mm, respectively. One can note typically malignant ELM features such as black dots, whitish veil, pseudopods, depigmentation area and an irregular pigment network (PN) developed on a pre-existent acquired moles and appeared during a six-month period. (d), *In situ* CM developed on a congenital nevus showing modification of PN within 3 months. (e and f), Cases of 2-mm diameter CM (0.3 and 0.2 mm, respectively) developed *ex novo* during 1 month. In these cases, features such as radial streaming (e) and pseudopods (f) along with a positive history (appearance *ex novo* in male patients >40 years within 4 weeks) permitted diagnosis of type 1 lesions.

significance of exposure at different times in life is controversial. However, exposure to intense solar radiation in youth seem to significantly increase lifetime risk of melanoma. A suspicious clinical history is associated with a lesion that has changed shape or dimension recently (typically during the six months before the visit).

Clinical evaluation. After a full body skin evaluation, CPLs are first classified by the ABCDE rules (asymmetry, irregular border, different colours, diameter >6 mm, and evolution) (22). If necessary, a naevus map is recorded (e.g. utilizing the Molemax II macro-camera) to allow more accurate evaluation of variations in lesions during follow-up (12).

After Step 1, all CPLs showing at least two ABCDE criteria and a suspicious family or clinical history should be evaluated by epiluminescence microscopy.

Step 2: ELM evaluation - first analysis. Preliminary ELM-evaluation should classify CPL as: (a), non-melanocytic lesions (such as angiokeratoma, verrucous naevus, pigmented basal cell carcinoma, seborrheic keratosis, angioma, keratoacanthoma, and solar keratosis and (b), melanocytic lesions [such as compound naevus, intradermal naevus, papillomatous compound naevus, Spitz naevus, blue naevus (without pigment network); junctional naevus, lentigo simplex, pigmented

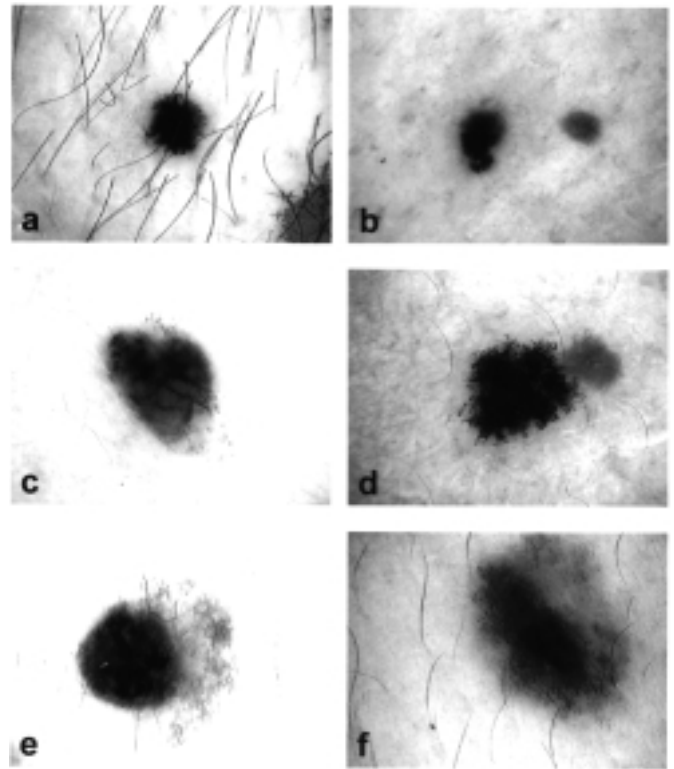


Figure 2. ELM images of type 2 lesions: all these lesions show perturbation of PN and some ELM features such as pseudopods and depigmentation areas typical of these kind of lesions. (a and b), The lesions were discovered respectively in lower limbs of a 38-year male and back of a 42-year woman; both lesions showed a suspicious history (little peripheral modification during last three months). (c-f), Lesions showed a pattern compatible with type 2 lesions but not a suspected history.

spindle cell naevus of Reed, naevus spilus, cockarde naevus, atypical naevus, malignant melanoma (with pigment network)].

In the group of non-melanocytic lesions surgical treatment is mandatory for pigmented basal cell carcinomas. In other cases, even if most such lesions are benign and do not need any therapy, a decision on treatment will ultimately depend on the kind of lesion, possible evolution to skin cancer and the patient's preference based on aesthetic and psychological grounds.

In the case of melanocytic lesions, further sub-classification is required to allow a therapy decision to be made.

Step 3: ELM evaluation - second level evaluation - risk-related classification of melanocytic lesions. Melanocytic lesions are classified as very low, low, medium, high and very high risk lesions on the basis of accurate assessment of structural and morphological parameters (Table I). The characteristic and classification of individual lesions is based on the presence or absence of typical ELM features (2-18): Type 1, very high risk. All lesions suspected of being melanoma because they demonstrate ELM-features typical for melanoma (Fig. 1).

Type 2, high risk. Atypical nevi or borderline lesions that present an irregular network and other features, such as pseudopods or radial streaming, that in most cases indicate the presence of atypia (Fig. 2).

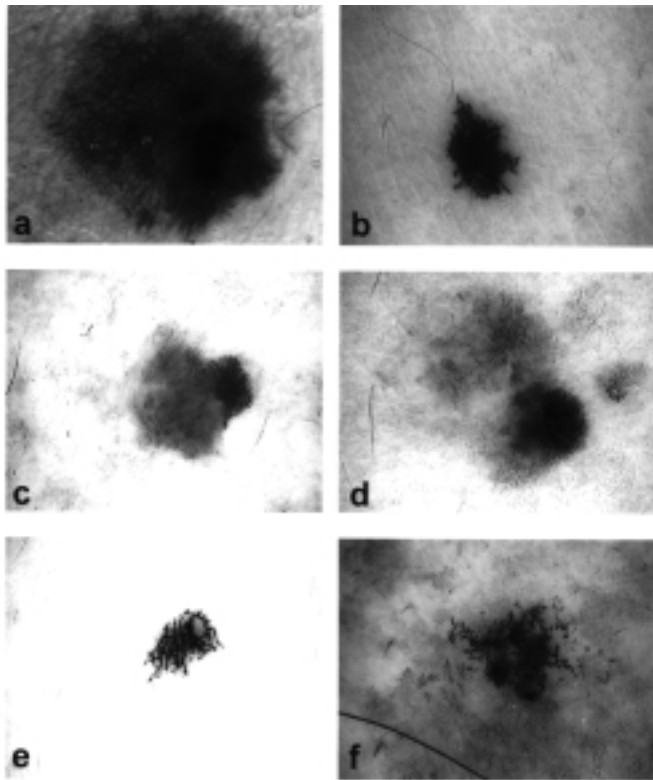


Figure 3. ELM images of type 3 lesions: all these cases represent lesions related to melanocytic hyperplasia without a suspicious history. Despite some irregularity of PN, all these lesions have remained stable for several years after an accurate evaluation of history. (a), A melanocytic hyperplasia on the breast of a 23-year woman. Such a lesion is frequently observed in young females and can be followed-up only. (b), Melanocytic hyperplasia on the back of a 38-year old woman. In this case too, the lesion appears unchanged during the years and the diagnosis of lentigo simplex is supported by the presence of a high frequency of lentigo solaris on the trunk. (c-f), Cases of melanocytic hyperplasia associated with lentigo solaris. (e and f), Lentiginous melanocytic hyperplasia. Despite the ELM image, lesions of this type can usually be managed by follow-up.

Table II. Working formulation of clinical use for the management of cutaneous pigmented lesions.

<ul style="list-style-type: none"> - Type 1 - Type 2 - Type 3 - Type 4 - Type 5 	}	<ul style="list-style-type: none"> A. With an <u>innocent</u> clinical appearance and clinical history B. With a <u>suspicious</u> clinical appearance and clinical history
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Type 3, medium risk. Lesions with a pigment network showing subtle perturbations that may be present in atypical naevi and lesions with melanocytic hyperplasia. This category includes lesions that are often misinterpreted. We have defined lesions which present only minor perturbations in the network ‘snakes in the grass’. The detection of slight alterations can generate difficulty in diagnosis, lead to overestimation of the seriousness of a lesion and unnecessary surgery. Clinical history and evaluation are important aids to avoiding such over diagnosis (Fig. 3).

Type 4, low risk. CPL with a benign appearing network (Fig. 4a and b).

Type 5, very low risk. Includes lesions with a benign appearing network and with a globular or other benign ELM pattern. This category includes the ELM patterns characteristic of compound nevi, and intradermal nevi (Fig. 4c and d).

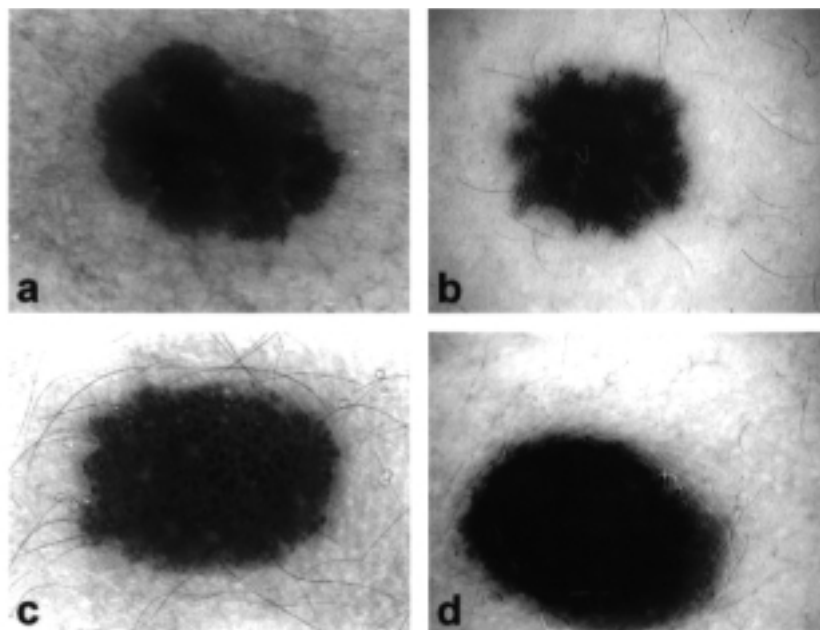


Figure 4. ELM images of type 4-5 lesions: (a), ELM features of a junctional nevus. (b), Lentiginous junctional nevus. (c) Compound nevus. (d), Blue nevus.

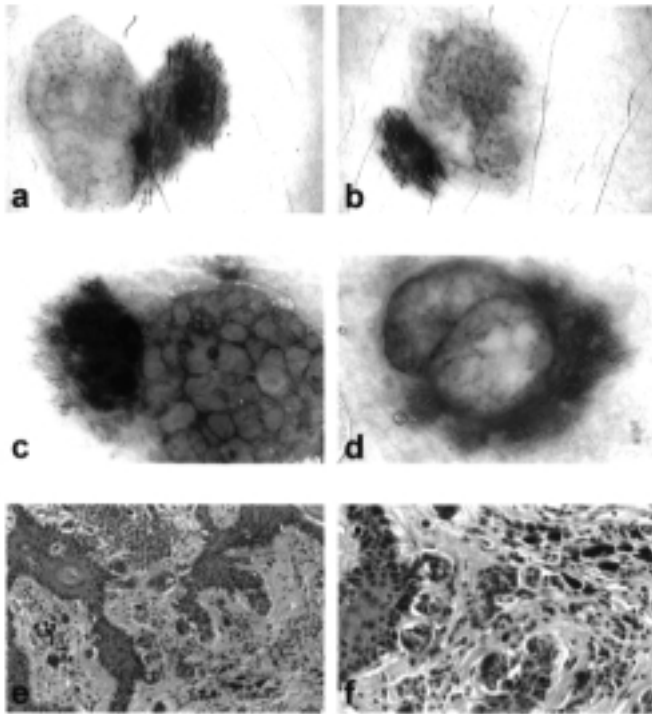


Figure 5. ELM images of type 5B lesions: (a-d), All cases of low risk lesions showing clinical modification during the preceding six months. (a and b), Intradermal naevi with a peripheral irregular PN indicating early transformation. (c), A melanoma arising near a verrucous nevus. (d), An atypical junctional proliferation arising at periphery of a papillomatous nevus. (e and f), Histological aspect of verrucous compound nevus (C) with atypical dermal melanocytic cells.

In terms of ELM criteria, this risk stratification does not differ substantially from the K&F classification (20), but

emphasizes clinical observations and additional parameters to facilitate better application of the K&F classification in clinical practice and standardize the management of CPL.

At the end of the first three steps, interpretation of ELM and other findings allows allocation of the lesion to follow-up or surgical treatment categories: (a), identification of a CPL as medium-risk in individuals with a suspicious history or, recent (ABCDE) variation in clinical features should be followed by surgical excision (subtype B in Table II; Fig. 5). (b), high- and very high-risk lesions should be treated surgically; and (c), patients with medium-risk lesions and no suspicious additional features should enter into a close follow-up program (subtype A in Table II).

Discussion

Management of patients with melanoma is complex requiring a multidisciplinary approach. The best protection against the development of melanoma is minimization of ultraviolet exposure. Early detection and timely surgical excision are critical to improved patient survival rates.

The accurate differential diagnosis of cutaneous pigmented lesions (CPLs) is an important first step toward early detection of cutaneous melanoma (CM). In previous studies (17,18), we evaluated the sensitivity and specificity of ELM (both sensitivity and specificity were high and statistically significant; $P < 0.0001$) as well as its role in the differential diagnosis of cutaneous pigmented lesions. We also evaluated the role of ELM in improving early diagnosis of CM by comparing ELM-based risk levels and the histology of surgically excised lesions. Screening activity during recent past years has indicated excellent agreement between of ELM findings and histological features (89%).

Here we highlight the importance of clinical features, especially recent change in CPLs, as a critical adjunct to the correct interpretation of the ELM features and the

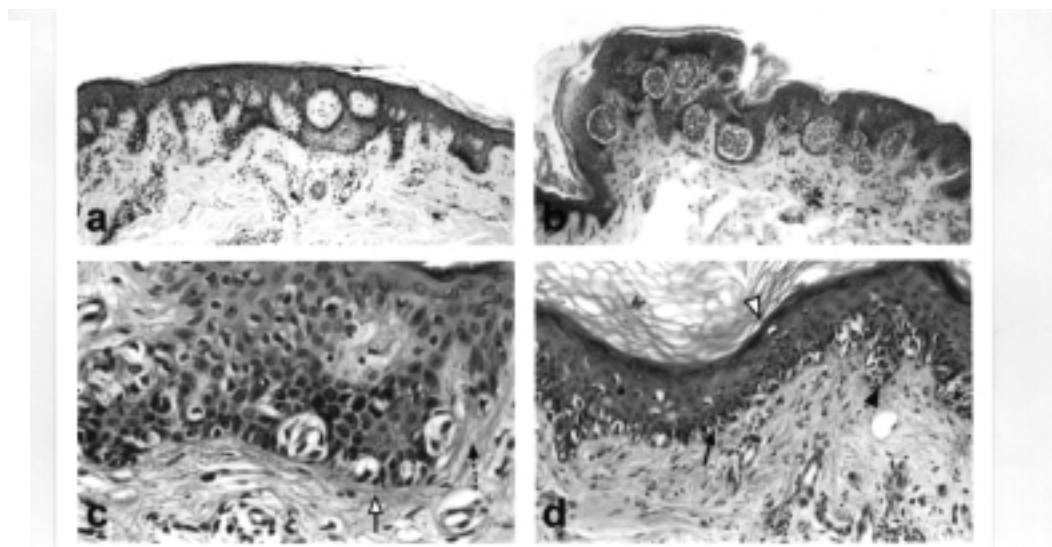


Figure 6. Histological findings of the main cutaneous pigmented lesions that produced a PN as an ELM feature. (a), Lentigo simplex. The melanocytic proliferation is predominantly in the basal layer (linear proliferation). (b), Junctional nevus. Nests due to melanocyte-derived cells at the epidermo-dermal junction. (c), Dysplastic nevus. Fusion of epithelial ridges with melanocytic component (open arrow) and lamellar fibroplasia subepithelia (broken arrow). (d), Melanoma *in situ*. Atypical melanocytic cells in the epidermis; three patterns: lentiginous (arrow), pagetoid (open arrowhead), and nested (closed arrowhead).

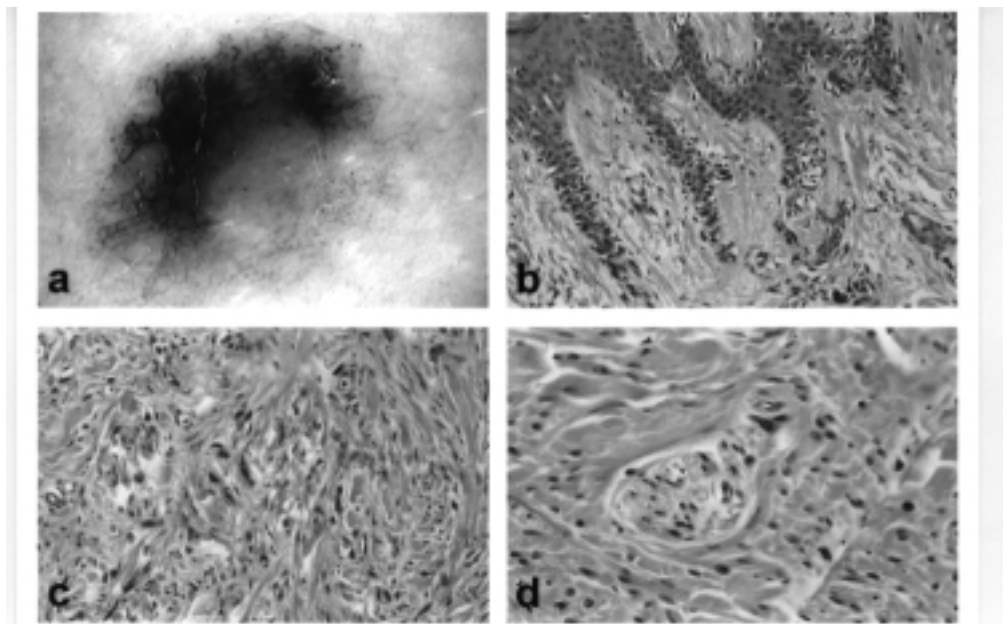


Figure 7. Desmoplastic melanoma. (a), ELM feature of a desmoplastic melanoma often misinterpreted as dermatofibroma and surgically excised after showing a modification with an irregular network at periphery. (b-d), Histological features of the lesion. (b), Abnormal melanocytes in the overlying epidermis. (c), In the dermis, population of spindle-shaped melanoma cells dispersed in collagenous coarse stromal bands. (d) The invading cells are associated with cutaneous nevus.

appropriate assignment of patients to surgery or follow-up.

During the past five years, both the improved experience of our ELM practitioners and increased screening activity have increased the sensitivity and specificity of the ELM approach. This has permitted increased detection of melanocytic lesions with a visible pigment network (types 1, 2, 3 and 4 of our risk-related classification) and increased the agreement between ELM and histology from 90 to 95%.

Although the reliability of ELM in clinical practice is widely recognized, classification of CPL using ELM-based criteria alone leads to misinterpretation of lesions that present minor perturbations of the pigment network (lesions that require follow-up, but not surgical excision) (Fig. 3). Correct diagnosis and classification of CPL is absolutely dependent on the combination of ELM-features with history and clinical observations. Some CPLs do not present the ELM pattern of a high-risk lesion (type 1 and 2) but have a suspicious history (significant changes in the preceding 6 months) and/or atypical clinical features (Figs. 1 and 6). Other lesions ['snake in the grass' lesions (17,18)] present slight modification of the pigmentary network (Fig. 3) that may cause difficulties in diagnosis and overestimation of risk. Such cases if treated surgically lower agreement between ELM and histology. In our experience, history and careful clinical evaluation can resolve these doubts. Our proposed classification (Table II) is a guide to the homogenization of interpretation of these lesions and to improvement of the diagnosis and treatment of CPL. It is important to limit surgery to CPLs that are truly malignant or have a high risk for malignance. We single out very high (type 1: suspected melanoma) and high (type 2: borderline or dysplastic lesion) risk lesions for biopsy. A type 1 lesion is immediately referred a surgeon for excision while a type 2 lesion is scheduled less acutely.

Both ELM evaluation and clinical parameters are important in deciding the fate of a lesion. Each main category may be further classified as A or B according to the presence or absence of a suspicious history and clinical evaluation.

For ELM-evaluation, the parameters described by previous authors have created a consensus that represents a highly valuable code of practice (2-18). These features represent the expression at the skin surface of particular distributions of melanocytes at the epidermal-dermal interface and, thus, particular histological features (Fig. 6). Collaboration between clinicians and pathologists is of utmost importance because in most cases the CPL are very small (<3 mm) (Figs. 1 and 2), or are lesions with atypical ELM alterations that are confined to the periphery of a benign lesion (Figs. 5 and 7). Such characteristics may affect a very limited area (<2 mm). An interdisciplinary approach to the management of CPL is critical to help pathologists optimally section tissue samples to include in the slide those structures which are clinically suspect and, to improve diagnostic accuracy. When histological examination is inconsistent with our clinical findings we discuss the dilemma with our pathologist. We agree strongly that 'diagnostic uncertainty requires a second opinion and that the degree of uncertainty must be disclosed to the contributing clinician' (23). Despite high sensitivity and specificity, ELM cannot be considered the sole criterion for the diagnosis of high-risk skin lesions. ELM features must be integrated with the appropriate clinical findings and a full and detailed history. Such strategy is central to the management of CPL. If there is doubt about a lesion, it should be excised and discussed with the pathologist because not all lesions neatly fit in any scheme and we have often seen lesions that are outside the bounds of any formal scheme.

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