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Folliculotropism in head and neck lentigo maligna and lentigo maligna melanoma

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Emi Dika[1,2], Martina Lambertini[1,2], Annalisa Patrizi[1,2], Cosimo Misciali[1,2], Federica Scarfì[1,2], Giovanni Pellacani[3], Victor Desmond Mandel[4,5], Francesca Di Tullio[3], Ignazio Stanganelli[4,5], Johanna Chester[3], Shaniko Kaleci[3], Daniela Massi[6], Vincenzo De Giorgi[7], Elisa Cinotti[8], Pietro Rubegni[8], Jean Luc Perrot[9], Francesca Farnetani[3]

(1) Division of Dermatology, Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Italy
(2) Department of Experimental, Diagnostic and Specialty Medicine (DIMES), Laboratory of Bioengineering, University of Bologna, Bologna, Italy
(3) Dermatology Department, University of Modena and Reggio Emilia, Modena, Italy
(4) Skin Cancer Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Meldola, Italy
(5) Dermatology Unit, Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy
(6) Section of Anatomic Pathology, Department of Health Sciences, University of Florence, Florence, Italy
(7) Section of Dermatology, Department of Health Sciences, University of Florence, Florence, Italy
(8) Department of Medical, Surgical and Neurological Science, Dermatology Section, University of Siena, S. Maria alle Scotte Hospital, Siena, Italy
(9) Dermatology Unit, University Hospital of St-Etienne, Saint-Etienne, France

Summary

Background: Lentigo maligna (LM) and lentigo maligna-melanoma (LMM) are histotypes of melanoma arising in skin with cumulative solar radiation damage. The extension of atypical melanocytes to the hair follicle (folliculotropism) is a histopathological feature of LM/LMM. Its role has not been totally clarified, but it may be correlated to treatment response in LM or to progression in LMM.

Objective: This retrospective, multicentric study aims to identify dermatoscopic features associated with folliculotropism in LMs/LMMs.

Patients and Methods: We analyzed cases of head and neck LMs/LMMs diagnosed between 2005–2014 at Melanoma Units, University of Bologna/Modena/Florence/Siena (Italy), Nice (France): 25 LMs and 73 LMMs were included.

Results: Grey circles (44 %) indicated an isthmic/bulb level of involvement, which were completely absent in the infundibular LM lesions (P = 0.041). In the group of LMMs, light/dark brown pseudonetwork and light brown structureless areas were an indicator of diffuse distribution of malignant melanocytes in the follicular units (P < 0.001 and P = 0.001, respectively), while grey circles indicated focal or diffuse distribution (P < 0.001).

Conclusions: A better understanding of the extension of malignant melanocytes is helpful, aiding clinicians in their decision to perform a radical excision or obtaining a biopsy in the most invasive area of the lesion, which includes potential folliculotropism.

Introduction

Lentigo maligna (LM) and lentigo maligna melanoma (LMM) are cutaneous histotypes of melanoma (MM) arising in skin with high cumulative solar radiation damage [1]. Lentigo maligna is an *in situ* melanoma with the potential to progress to an invasive LMM. Estimates suggest that the proportion of LMs that evolve to LMM is low, with a lifetime risk around 5 % [2]. However, rapid progression of LM to a deeply invasive tumor has been reported [2] and LMM represents 4–15 % of all invasive cutaneous MMs [3].

Lentigo maligna and LMM typically arise in the head and neck region (HNR) of older patients. Signs of chronic sun damage and photoaging are usually observed, including multiple solar lentigos, wrinkles, drooping skin, dark spots, leathery texture of the skin, telangiectasias and mottled pigmentation. The differential diagnosis between LM and other chronic ultraviolet (UV) induced pigmented or non-pigmented lesions may be challenging in some cases. Lentigo maligna clinically manifests as a solitary macule of slow growth with a great variation in color (tan-brown, black and even pink areas) (Figure 1a). Contiguous solar lentigos and pigmented actinic keratosis are reported to be present respectively in 30 % and 24 % of cases [4]. To perform a correct differential diagnosis, some dermatoscopic criteria of malignancy have been defined, such as the presence of grey color, asymmetrical pigmented follicles, rhomboidal structures, obliterated follicles, blue or white areas, granular pattern and grey dots [5, 6] (Figures 1, 2). In those areas with a functional and esthetic impact, reflectance confocal microscopy (RCM) is a good option in adjunct to clinical and dermatoscopic evaluations. Reflectance confocal microscopy is a second-level non-invasive diagnostic option shown to be highly accurate in the diagnosis of pigmented lesions, though one of its drawbacks is the longer examination duration [7].

At histology, LM is characterized by the proliferation of atypical melanocytes, mostly in single units, within the epidermis with absent or minimum pagetoid spread. Elastosis, due to chronic actinic damaged skin, and melanophages are commonly observed. Lentigo maligna-melanoma shows atypical melanocytes in single units and nests with dermal

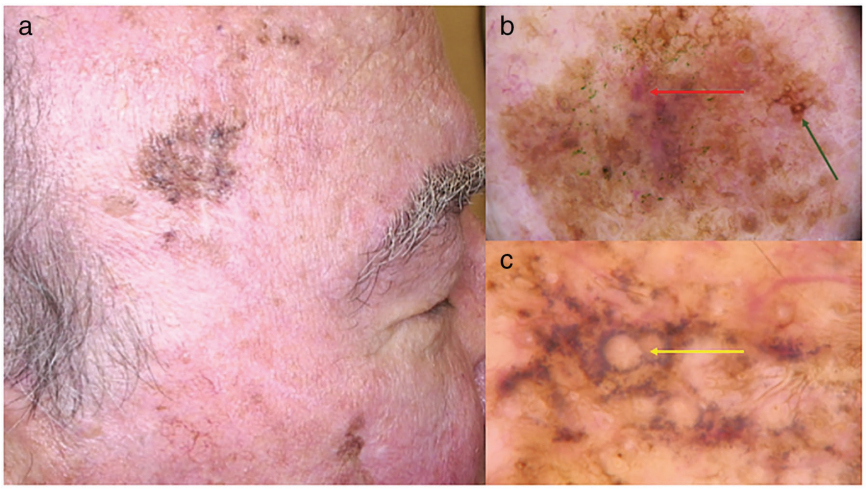

Figure 1 Clinical (a) and dermatoscopic presentation (b, c) of a lentigo maligna melanoma showing typical dermatoscopic features: asymmetric pigmented follicular openings (green arrow), grey circles (yellow arrow) and red areas (red arrow).

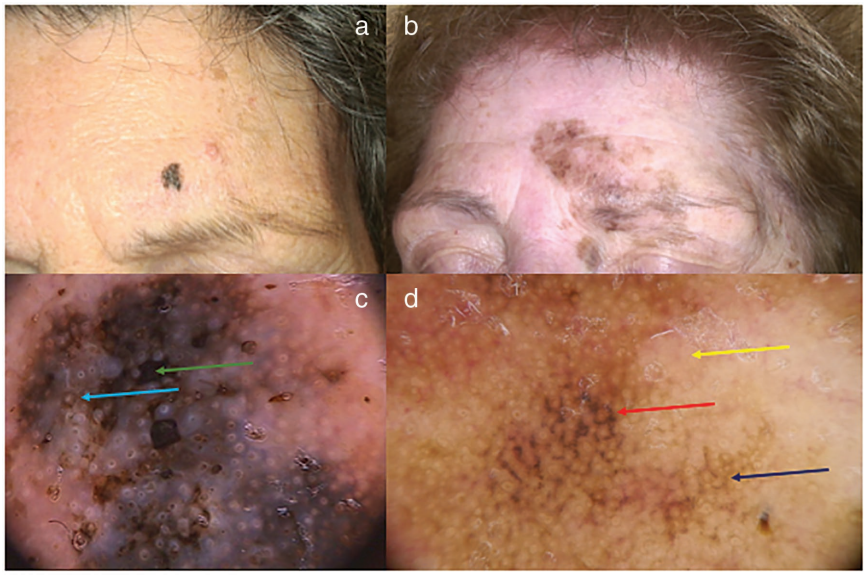

Figure 2 Clinical (a, b) and dermatoscopic (c, d) presentations of a lentigo maligna melanoma showing light/dark brown pseudonetwork (dark blue arrow), structureless areas (yellow arrow), asymmetric pigmented follicular openings (light blue arrow), grey circles (red arrow) and dark rhomboidal structures (green arrow).

extension [8, 9]. The extension of atypical melanocytes to the hair follicle, termed folliculotropism, has been described in MM and it is a characteristic feature of LM/LMM. However, its role has not been totally clarified [8, 10, 11]. Some authors advanced the hypothesis that the hair follicle represents a physical and immunologic barrier to the tumor spreading [12], while others [13–15] considered it as a feature enhancing the development of MM progression.

Other authors correlated the histopathologic feature of folliculotropism in the head-and-neck region (HNR) LM to treatment response and recurrences: indeed, it may be an obstacle to the success of tissue-sparing surgical techniques, topical drugs or radiotherapy [15]. It has even been proposed that a safety margin may not be needed for *in situ* melanomas if the excision margins are completely examined by histopathology [16].

As dermatoscopy is the most commonly used diagnostic tool in everyday practice and dermatoscopic parameters have not been previously correlated with folliculotropism, the current retrospective, multicentric observational study aims to identify dermatoscopic features associated with folliculotropism extension in HNR LMs and LMMs.

Materials and Methods

Study design and patient selection

We retrospectively analyzed registered cases of patients with HNR LMs and LMMs diagnosed between January 2005 and December 2014, at the Melanoma Units and Laboratories of Dermatopathology, University of Bologna, Modena, Florence, Siena (Italy) and Nice (France). Lesions showing a predominance of smaller cells at histology with an absence of solar elastosis or presence of single elastic fibers only, were classified as presenting a lentiginous pattern of superficial spreading MMs and were therefore excluded. Mucosal and ocular MMs were also excluded. Patients were classified according to LM or LMM diagnoses.

The study protocol was approved by the local ethics committee (DERM-MTC 2017).

Clinical and dermoscopic analysis

Clinical data were evaluated for each group, including sex, age at diagnosis, the anatomic site and characteristics of the tumor. Anatomic sites of lesions were classified as scalp, face (including forehead, nose and cheeks) and neck.

Further inclusion criteria were lesion diameter, ranging from 1 cm to 2 cm (± 0.1–0.2 cm) and conventional surgical excision, respecting a surgical margin of 0.5 cm ± 1 cm. The study criteria specified the exclusion of mucosal and ocular MMs as well as lesions of the ears and eyelids (low density of follicles) and patients treated with Mohs surgery (horizontally cut sections do not include sufficient information on hair follicle histopathology) [17].

All dermatoscopy images were retrieved from the clinical archives. Dermatoscopic images (x 20 and x 40 magnification) were obtained with a FotoFinderMedicam 800HD (Fotofinder, Germany), with alcohol-gel as linkage fluid. Seven dermatoscopic parameters were assessed, including *(1)* light/dark brown pseudonetwork, *(2)* dark/grey rhomboidal structures, *(3)* grey circles, *(4)* asymmetric pigmented follicular openings, *(5)* blue dots, *(6)* light brown structureless areas and *(7)* red areas.

Histological analysis

Formalin-fixed, paraffin-embedded tissue sections of MM samples were obtained with institutional review board approval. Histological slides of primary and recurrent lesions were recovered and reviewed retrospectively by three expert dermatopathologists (DM, CM, JLP). Prospective LM and LMM diagnoses were confirmed and LM diagnosis was defined according to previously described characteristics [18], including an increased number of atypical and enlarged melanocytes irregularly positioned along the basal layer of the epidermis with occasional agglomeration in files, involvement of the adnexal epithelia and moderate solar elastosis in the dermis. Breslow thickness, ulceration, mitosis, tumor infiltrating lymphocytes (TIL) and lymphovascular invasion were annotated for each case.

Slides were further reviewed for the presence of malignant melanocytes, the distribution and level of involvement in follicular units and severity of solar elastosis. The distribution of the melanocytes was classified as *(1)* absent – no involvement; *(2)* focal – involvement in < 3 follicular units per specimen; *(3)* diffuse – involvement in ≥ 3 follicular units per specimen [10]. The level of involvement of atypical melanocytes (both lentiginous or nested) in the follicle unit was categorized as extending into the *(1)* infundibulum; *(2)* isthmus; *(3)* bulb [14].

The severity of solar elastosis was categorized as *(1)* absent; *(2)* mild – increased elastic fibers in the upper dermis, with incremented width; *(3)* moderate-thickened elastic fibers with a disarranged orientation in the upper dermis; and (*4*) severe – serpiginous and thickened elastic fibers, constituting most of the upper dermis [19].

Statistical analysis

Analysis was performed with the STATA program, version 14 (StataCorp LP 4905 Lakeway Drive College Station, Texas 77845 USA). Numerical data were expressed as mean and standard deviation or median and range, as appropriate. Qualitative data were expressed as frequency and percentage. The chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables, whilst statistical differences for continuous variables for the two groups were examined using the Student's t test. Multivariate analysis was performed using logistic regression for the significant factors identified with univariate analysis; lesions were grouped according to infundibular, isthmic/bulge or bulb involvement. The results were expressed as odds ratio (OR) with a 95 % confidence interval (CI). A P value < 0.05 was considered significant.

Results

A total of 25 LMs and 73 LMMs met the inclusion criteria and were included in the current study. They were assessed according to their dermatoscopic and histopathological features, including folliculotropism distribution and involvement. Most patients were male (61 %) and most lesions were located on the face (69 %). Analysis confirmed that the distribution of dermatoscopic patterns is different between LM and LMM. The dermatoscopic features of light/dark brown pseudonetwork, asymmetric pigmented follicular openings and blue dots were statistically different between LM and LMM. The observations of light/dark brown pseudonetwork and asymmetric pigmented follicular opening were associated with LM (92 % and 92 % respectively) whilst they were only observed in around half of the LMM lesions (P = 0.004 and P < 0.001, respectively). Almost all the blue dots registered were associated with LMM diagnoses (resulting in a statistically significant difference between their presence in LMM (20 %) and LM (4 %; P = 0.016). Histopathological assessment of LMs revealed severe solar elastosis in more than two-thirds of the LM lesions. The mean Breslow thickness for the LMM group was 1.2 mm (± 2.17; range 0.1–10). Tumor infiltrating lymphocytes were present in 62 % of the lesions (n = 45), ulceration was reported in five lesions, and regression in almost a third of the lesions (n = 22; 30 %). Demographic characteristics, dermatoscopic and histopathological features are outlined according to histopathology diagnoses in Tables 1, 2 (online supplement only).

The correlation of dermatoscopic features with LM follicular distribution and level of involvement revealed that the presence of grey circles (44 % of the cases) indicated an isthmic or bulb level of involvement, whilst being completely absent in the infundibular LM lesions (P = 0.041). A similar trend (although not statistically significant) was observed with the grey rhomboidal structures; mainly absent in infundibular LM lesions, and more represented in the isthmic and bulb LM lesions (P = 0.082). Blue dots were observed in a single LM, which was one of the two LMs with bulb involvement in this cohort (P = 0.005) (Table 3; online supplement only). Of the dermatoscopic features assessed in this study, none were correlated with LM follicular distribution (Table 4, online supplement only).

Conversely, in the group of LMMs, the level of follicular involvement was not correlated with any of the dermatoscopic features assessed in this study (Table 3, online supplement only), but with the distribution of malignant melanocytes in the follicular units. The detection of the light/dark brown pseudonetwork and light brown structureless areas was an indicator of diffuse distribution (P < 0.001 and P = 0.001, respectively), and the presence of grey circles indicated either

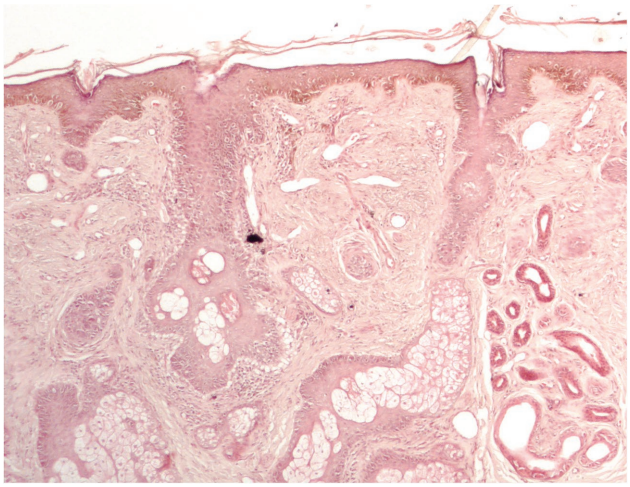

Figure 3 Histopathological slide of a lentigo maligna (hematoxylin-eosin stain, original magnification x 10). It shows a proliferation of atypical melanocytes in the epithelium of the follicular unit.

focal or diffuse distribution ($P < 0.001$) (Table 4, online supplement only).

Discussion

Folliculotropism has been recently identified in almost 96 % of LM lesions evaluated at histopathology [20] (Figures 3, 4) and it has been described as a specific differentiating feature from pigmented actinic keratosis with reflectance confocal microscopy [21]. The high prevalence of folliculotropism in LM and LMM has been confirmed in the current study. However, the pathogenesis of LM/LMM and the role of folliculotropism is not fully understood. Indeed, some authors have advanced the hypothesis that growth factors involved in the hair cycle, residing in the isthmic and bulge region of the hair follicles, may produce chemotactic or proliferative effects on melanocytes, while suppressing apoptosis [22–27]. The underestimation of malignant melanocytes in the hair follicle in LM and LMM treatment is believed to be associated with high recurrence rates [14, 20].

Some authors have recommended that folliculotropism should be included in histopathological reports, as it may be correlated with eventual treatment efficacy [14]. Nevertheless, these characteristics are not routinely applied in clinical practice [10, 14].

Dermatoscopy is the most commonly used evaluation tool for clinical surveillance [5, 28–37], but the correlation of dermatoscopy features and folliculotropism has not yet been investigated. Dermatoscopic features associated with LM diagnosis are not specific. Tiodorovic-Zivkovic et al. reported that the most sensitive features for recognition of LM by dermatoscopy are grey circles and grey rhomboids [5] and this study confirms their presumption, with all evaluated LMs showing these dermatoscopic features. However, these features are associated with many types of benign and malignant non-melanocytic lesions [20]. The dermatoscopic detection of grey circles has previously been presented in the literature as a differential feature for the diagnosis of LM from pigmented actinic keratosis [6] and it has been claimed to represent the strongest indication of LM diagnosis [5]. In the current study grey circles were observed in almost half of the LM lesions and were found to be statistically associated with a deeper (isthmus and bulb) level of follicular involvement. The observation of grey circles in LMM was associated with focal or diffuse distribution. This observation is in agreement with the hypothesis that the visualization of grey circles in LM by dermatoscopy probably arises from stem cells of the hair bulge located in the nearby isthmic region [36, 38]. Furthermore, the observation of a light/dark brown pseudonetwork and light brown structureless areas was associated with focal and diffuse LMM distributions.

Solar elastosis is a histologic sign of sun damage [19] and it was observed in all LM cases analyzed and classified as severe in 68 %. This finding confirms the pathogenetic role of UV radiation in LM and LMM and contributes to the understanding that this tumor has a stronger propensity for subclinical extension.

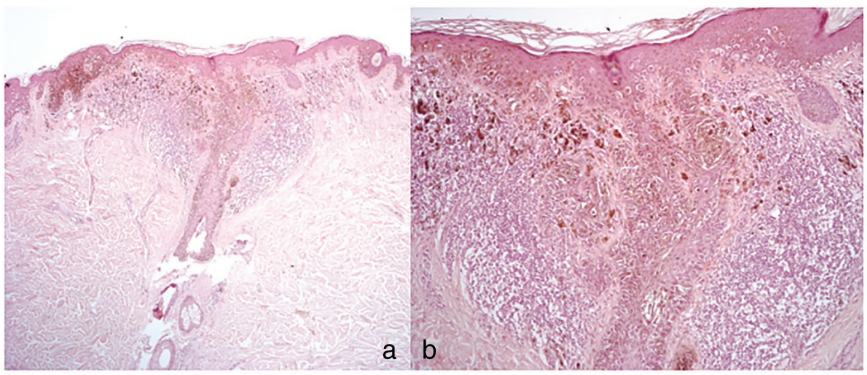

Figure 4 Histopathological slides of a lentigo maligna melanoma (hematoxylin-eosin stain, original magnification x 10 (a), x 20 (b)). They show a proliferation of atypical melanocytes in the dermis and in the epithelium of the infundibulum and isthmus of the follicular unit.

This study is limited by the small sample size and the quantity of missing data. Of particular note are the limited findings of dermatoscopic features associated with LMM level of follicular involvement and LM distribution. Furthermore, the biological characteristics of LM/LMM and the pathogenetic factors that may contribute to treatment outcome were not investigated. These findings need to be confirmed in larger series and represent only preliminary results.

Conclusions

The presence in dermatoscopy of grey circles in LM is associated with an increased probability of an isthmic or bulge follicular extension of malignant melanocytes, while the presence of grey circles, a light/dark brown pseudonetwork and light brown structureless areas in LMM correlates with the distribution of malignant melanocytes in the follicular units (focal/diffuse). Our study shows dermatoscopic parameters that may predict follicular involvement in LM and LMM. Additionally, the detection of grey circles may assist the clinician to perform a radical excision or to obtain a biopsy in the most invasive LMM area.

Correspondence to

Emi Dika, MD, PhD
Department of Experimental, Diagnostic and Specialty Medicine
University of Bologna

Via Massarenti 1
40138 Bologna, Italy

E-mail: emi.dika3@unibo.it

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