Impact of Dermoscopy and Reflectance Confocal Microscopy on the Histopathologic Diagnosis of Lentigo Maligna/Lentigo Maligna Melanoma

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Background: Equivocal pigmented lesions of the head are usually biopsied to avoid inappropriate treatment. Clinical approach has evolved from simple visual examination to sophisticated techniques for selecting the biopsy sites.

Objective: This study aimed to retrospectively evaluate the efficiency of dermoscopy (DE) and reflectance confocal microscopy (RCM) in sampling a histopathologically representative focus of lentigo maligna/lentigo maligna melanoma.

Methods: Punch biopsies and surgical excisions of 72 patients, 37 men and 35 women (median age 70.6 years, range 39–90 years), affected by lentigo maligna/lentigo maligna melanoma of the head, sent from a single dermatology clinic, were reviewed for the presence of 5 histopathologic criteria: atypical junctional melanocytes, increased junctional melanocytes, follicular colonization, pagetoid spread and melanocytic junctional nests, plus other minor features. Forty-two patients were biopsied under DE and 30 under RCM guidance.

Results: Accuracy of the 2 techniques in sampling a representative tissue overlapped in most cases, although RCM selected sites to biopsy with more histopathologic criteria, in particular pagetoid spread and melanocytic nests. Interestingly, with RCM, inflammation and melanophages were observed more in biopsy than in excision. False positive cases were not registered.

Conclusion: Compared with the sampling at naked eye, our results show that DE and RCM help selecting the most appropriate areas for biopsies, thus allowing not only more robust histopathologic diagnoses, but also a more accurate microstaging of tumor.

Key Words: lentigo maligna, melanoma, histopathology, dermoscopy, reflectance confocal microscopy

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INTRODUCTION

Pigmented lesions on sun-damaged skin represent difficult entities to diagnose for clinicians, given their overlapping features.[1] Nevertheless, it is important to identify malignant melanoma in an early phase to ensure the best treatment and prognosis for the patient.[2] Currently, excisional biopsy is the recommended diagnostic procedure for lentigo maligna (LM) and LM/melanoma (LMM).[3] However, to avoid esthetic damage in cosmetically sensitive areas and offer a diagnosis close to certainty, a previous biopsy is recommended.[4] In the past, simple visual inspection was the method to select the focus to sample. In a dermatologists' survey, the most frequent clinical criteria of biopsy resulted: darkest area, indurated or papulonodular area, and referring changed area.[5] This method at naked eye, applied in a study of 46 melanocytic lesions on sun-damaged skin by Somach et al,[5] resulted in 40% of cases containing more histopathologic features in excisional specimens than biopsies; in particular, dermal invasion at biopsy was a feature missed in approximately 20% of cases.

The simple visual method has been replaced nowadays by more sophisticated techniques. Dermoscopy (DE) and reflectance confocal microscopy (RCM) have evolved until becoming valid diagnostic tools for dermatologists. Dermoscopic[6–8] and confocal criteria[9,10] have been developed for the diagnosis of melanoma, taking into account histopathology as the gold standard; nevertheless, no studies have been made to evaluate the impact of these techniques on the routine work of pathologists, in terms of diagnostic confidence and accurate presurgical staging of tumor.

This study was designed to determine the efficiency of DE and RCM in sampling representative foci of LM/LMM in suspicious pigmented lesions, particularly from the head. The difference between the 2 techniques was investigated by evaluating the presence and the number of histopathological features consistent with LM/LMM observed in punch biopsy and in corresponding surgical specimens; moreover, the accuracy of microstaging made on biopsy as compared to the excision was evaluated.

MATERIALS AND METHODS

All cases of LM/LMM of the head diagnosed in the period 2007–2015 were retrieved from our archives, then those cases in which a 4- or 5-mm punch biopsy was performed to obtain a presurgical diagnosis, and for which we also possessed the surgical specimens, were selected. To obtain a homogeneous group of patients, we included in the study only those examined at, and sent to us, by a tertiary referral Dermatology Clinic, where DE and RCM are

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currently used, and that retrospectively gave us information about the technique (DE or RCM) used for each case (see Acknowledgments).

A total of 72 patients showing all the above requisites were collected. Patients were 37 men (51.4%) and 35 women (48.6%). The median age was 70.6 years (range 39–90 years); 62 patients (86.1%) were older than 60 years, whereas only one patient (1.4%) was younger than 40 years. This population was divided into 2 subgroups according to the technique used to determine the site to biopsy: 42 cases (58.3%) studied with DE and 30 (41.7%) with RCM.

All punch biopsies and surgical specimens were reexamined at the microscope by 2 of us (E.M. and A.M.C.), aware of the clinical suspicion, but blind to clinical, dermoscopic, or RCM images. Deeper sections and immunohistochemical staining (S-100 protein, Melan-A, MiTF, and HMB-45), performed in selected cases, were also reviewed.

All cases were evaluated for the presence of 5 major histopathologic criteria consistent with LM/LMM: atypical junctional melanocytes, increased junctional melanocytes, follicular colonization by melanocytes, pagetoid spread, and melanocytic junctional nests. Other histopathologic features, including solar elastosis, epidermal hypertrophy and atrophy, basal keratinocytes' hyperpigmentation, melanophages, and inflammation in papillary dermis, were also evaluated. The presence of dermal invasion and of any coexistent benign or nonmelanocytic lesions was also registered both in punch biopsies and surgical excisions.

A SPSS software, version 14.0.1 (SPSS, Inc, Chicago, IL), was used for statistical analysis. Comparison of data between groups was performed by Pearson's χ^2 test. A $P < 0.05$ was considered statistically significant.

The study was conducted in accordance with the precepts of the Helsinki Declaration, and all data were handled anonymously according to the national laws.

RESULTS

Dimensions of lesions ranged between 0.2 and 4.5 cm (median 1.7 cm), with a similar distribution between male and female patients. The lesions were localized mostly on the face (52 cases, 72.2%), followed by scalp (10 cases, 13.9%), orbital region (7 cases, 9.7%), and upper lip (3 cases, 4.2%). The original diagnosis on punch biopsy, before revision, was fully consistent in 61 cases and probable in 8 cases, for LM or LMM. Three cases, belonging to the DE group, initially considered not diagnostic, resulted consistent with LM (2 cases) and probable LM (1 case) after revision. Histopathologic diagnoses on biopsies and surgical excisions are reported in Table 1. In 2 cases, no residual tumor was found at surgical excision; 1 case was an in situ lesion (Fig. 1) and 1 a superficially invasive melanoma (Fig. 2). In these 2 cases, surgical specimens were thoroughly included, multiple sections were made, then the tissue was flipped and reembedded; further levels were cut, and also immunostains were performed, excluding the presence of residual tumor. Only foci of solar lentigo were found in both cases.

Among the immunohistochemical stains, Melan-A and MiTF demonstrated to be the most useful in highlighting atypical basal melanocytes, whereas S-100 protein contributed to enhance dermal invasion in 3 cases of desmoplastic melanoma.

TABLE 1. Diagnoses Made on Punch Biopsies and Surgical Excisions After Revision

	DE Cases		RCM Cases	
	Biopsy	Excision	Biopsy	Excision
Consistent LM	30	33	20	21
Probable LM	6	0	3	0
LMM	6*	8*	7†	8†
Not diagnostic	0	0	0	0
No residual lesion	0	1‡	0	1§
Total	42	42	30	30

*One case of desmoplastic melanoma.
†Two cases of desmoplastic melanoma.
‡One in situ melanoma.
§One superficially infiltrating melanoma.

Benign and/or nonmelanocytic lesions, in few cases multiple, were found in association with a high percentage of LM/LMM. They were more frequently observed in excision (73.6% of cases) than in biopsy (17.7%), and they were mainly represented by solar lentigo and actinic keratosis, followed by seborrheic keratosis and dermal nevi (data not shown).

By evaluating the distribution of major histopathologic criteria in biopsy and excision, in the 2 groups, biopsies DE guided showed less-frequent melanocytic nests and pagetoid infiltration as compared to complete excision, although differences were not statistically significant (Table 2). Evaluation of minor features resulted in melanophages more frequent in biopsies than in excisions, particularly with RCM. Moreover, biopsies RCM guided showed more frequent inflammation than in excisions, but again difference was not statistically significant (Table 3).

Overall, RCM allowed the selection of biopsies showing statistically more robust histologic criteria, in particular a total of 22 cases of 30 (74%) RCM-guided featured 4 to 5 major criteria versus 22 cases of 42 (57%) biopsied with DE guidance ($P = 0.005$) (Table 4). Moreover, RCM resulted more sensitive in selecting the area to biopsy; in fact, punch biopsy showed more criteria than complete excision in 23.3% of cases, as compared to 16.7% for DE cases ($P = 0.04$) (Table 5).

Results obtained in this study compared with those of Somach's study,[5] are shown in Table 6. In comparison with biopsy made at naked eye, overall biopsies made under DE or RCM guidance showed the same number of histopathologic criteria found in excision in a higher percentage of cases (67% vs. 54%), together with features more consistent with LM/LMM (20% vs. 11%). Moreover, presurgical staging resulted much more accurate; in cases in which biopsy showed only an in situ lesion, a lower percentage of infiltrating melanomas was found after excision (8% vs. 20%), whereas, among cases of infiltrating lesions, a higher percentage of cases were already found in biopsy (14% vs. 7%) ($P = 0.01$).

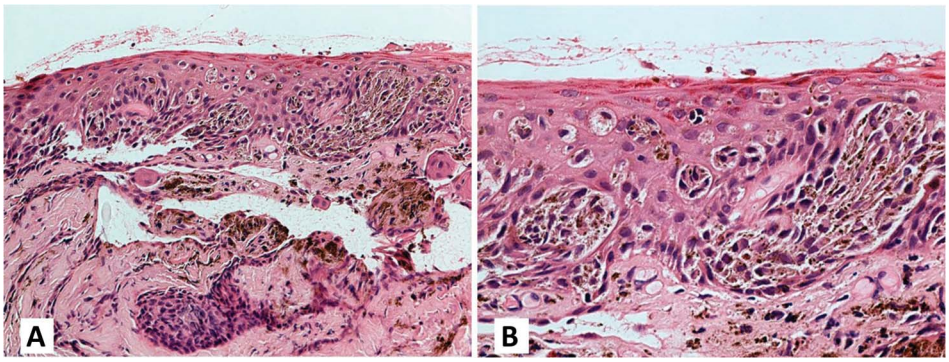

FIGURE 1. A case of LM completely removed by punch biopsy: Atypical melanocytic nests on the forehead of a 78-year-old woman (A, H&E, ×200; B, H&E, ×400).

DISCUSSION

Histopathologic diagnosis of LM/LMM can be very difficult when a small punch biopsy is available but of paramount importance to avoid esthetic damage[4] and to ensure the best prognosis for the patient.[11,12] The guidelines recommend a complete excision for the histological diagnosis of LM/LMM,[3] but there has been a progressive increase of incisional biopsies in suspected pigmented lesions, especially in cosmetically sensitive areas.[12] Pitfalls of an incisional biopsy are represented by sampling error, an uncertain diagnosis and microstaging inaccuracy.[12] The management of pigmented lesions has changed over time, thanks to technological progress. The simple visual method has been replaced by more sophisticated techniques, such as DE and RCM. Taking into account, histopathology as the gold standard, dermoscopic,[6–8] and confocal criteria[9,10] have been developed for the diagnosis of melanoma. Nevertheless, the impact of these techniques on the routine work of pathologists has never been evaluated, until now.

This study aimed to evaluate the efficiency of DE and RCM in sampling a focus of tissue from suspected pigmented lesions of the head. We retrospectively revised a homogeneous population of patients evaluated clinically in a tertiary referral Dermatology center, with known expertise in DE and RCM.

The results of our study demonstrated that biopsies made under DE or RCM guidance allowed us to make a confident or probable diagnosis of LM/LMM in all cases. The 3 cases in which a descriptive, not diagnostic, diagnosis was previously made by other pathologists, after revision showed enough criteria to permit a confident diagnosis in 2 cases, and a probable diagnosis in another case, implying that the level of diagnostic confidence in a particular setting is not the same for all pathologists, depending on the personal expertise. Interestingly, the 3 patients underwent surgical excision, which showed clearly an LM afterward, therefore clinicians can decide to perform surgery in selected cases, even with a histopathologically uncertain diagnosis, when facing a particularly worrisome lesion.

The 2 methods demonstrated a high level of sensitivity in discovering most histopathologic criteria, although RCM provided biopsies with more robust criteria of LM/LMM, as compared to DE.

Among the articles addressing the dermoscopic–pathologic correlation of melanocytic proliferations, particularly on sun-damaged skin,[6–8,13] a recent one made a point-by-point

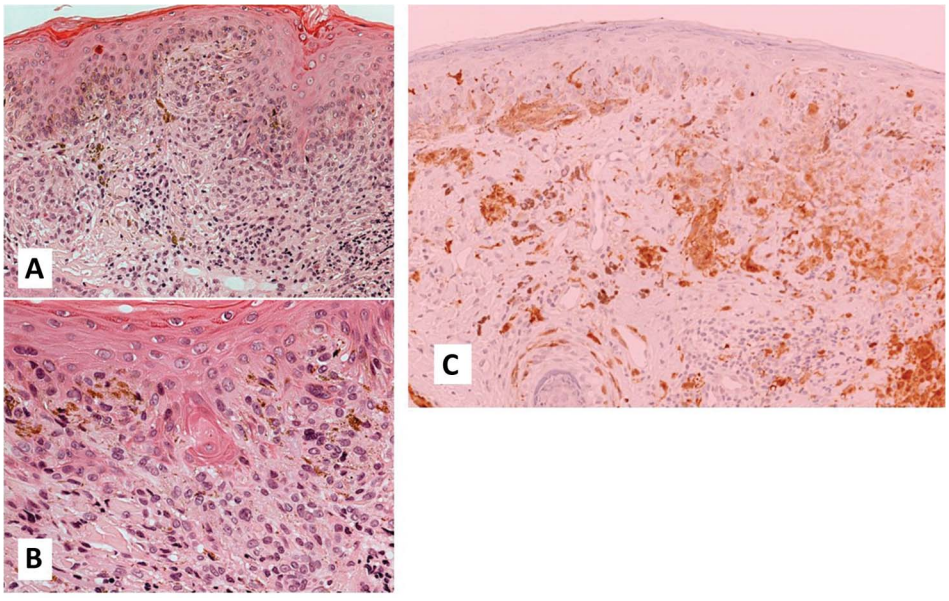

FIGURE 2. An LMM on the nose of a 39-year-old woman, completely removed by punch biopsy (A, H&E, ×200; B, H&E, ×400); S-100 protein immunostaining highlighting dermal invasion (C).

TABLE 2. Distribution of Major Histopathologic Criteria in Punch Biopsy and Excision in DE Group and RCM Group

	DE (42 Cases)		RCM (30 Cases)	
Major Histologic Criteria	**Biopsy (%)**	**Excision (%)**	**Biopsy (%)**	**Excision (%)**
Atypical melanocytes	42 (100)	39 (92.8)	28 (93.3)	28 (93.3)
Increased melanocytes at dermoepidermal junction	41 (97.6)	39 (92.8)	29 (96.7)	28 (93.3)
Adnexal colonization by melanocytes	33 (78.6)	33 (78.6)	25 (83.3)	23 (76.7)
Melanocytic nests	23 (54.8)	30 (71.4)	19 (63.3)	20 (66.7)
Pagetoid infiltration	19 (45.2)	23 (54.8)	17 (56.7)	16 (53.3)

P, not significant.

correlation between cases of LM and solar lentigo.[13] In this study, light-brown pseudonetwork corresponded to atypical melanocytes' proliferation, and in our cases, indeed, atypical and proliferating melanocytes were visible in almost all punch biopsies studied by DE. On the other hand, since light-brown pseudonetwork can be due, also, to proliferation of pigmented keratinocytes, this parameter was considered not useful in the differential diagnosis.[13] The presence at DE of irregular brown globules on a light-brown pseudonetwork, corresponding histologically to the presence of nests of atypical melanocytes at the dermoepidermal junction, seemed highly specific of LM.[13] In our cases, nests were found less frequently in biopsies (54.8%) than in excisions (71.4%), suggesting that this parameter was missed in several cases. The dermoscopic feature of dark-brown/blue-gray ribbon-like structures, due to the accumulation of numerous melanophages, resulted highly specific of LM.[13] In our cases studied with DE, melanophages were present more in punch biopsies than in excisions (88% vs. 80.9%), suggesting that dermoscopists used this parameter in selecting the site of biopsy. Asymmetric pigmentation of follicular ostia is also considered a highly specific dermoscopic finding in LM, corresponding to irregularly shaped nests of atypical melanocytes arranged along the follicular infundibulum, whereas symmetric pigmentation is due to the increased number of solitary melanocytes in follicular infundibulum.[13] In our cases, follicular colonization by melanocytes, either in singular units or in nests, was observed in 78.6% of cases at DE, both in biopsies and in excisions, implying that this parameter was not missed at DE inspection.

Compared to DE, RCM is considered a more sensitive technique that provides a horizontal visualization of a skin lesion with a cellular level resolution, allowing for the recognition of melanocytes. Melanocytes can appear round to oval, but also fusiform or dendritic in shape, with melanin pigment constituting a natural contrast.[14] In our cases, indeed, melanocytic nests and pagetoid infiltration were visible with RCM roughly in the same number of cases in biopsy and excision. Among minor histopathologic features, inflammation and melanophages were more frequently found in punch biopsy than in excision with RCM. This can be partly expected because it has been reported that RCM is able to visualize inflammation, in form of small bright round structures (<20 μm) without visible nucleus,[15] and that inflammation, although observed in up to 60% of benign lesions in one study, has been reported almost always in melanoma.[16] On the contrary, the presence of melanophages, more evident in biopsy than in excision, seem to hamper the diagnostic value of RCM, representing a potential pitfall in the selection of site to biopsy. RCM structures corresponding histopathologically to melanophages have been described as plump-bright cells in papillary dermis, larger than 20 μm, irregularly shaped, with ill-defined borders and usually no visible nucleus, sometimes in aggregates.[15] On the contrary, melanocytes in the dermis appear as nucleated, roundish to oval refractive cells, isolated, or clustered.[17] These cells, often together with plump cells corresponding to melanophages, are responsible for the so-called blue-whitish veil that characterizes mostly melanomas.[17] Because dermal melanocytes were present in a small percentage of our lesions, it is possible that clusters of melanophages were suspected, in a number of cases, to be foci of infiltrating melanoma.

TABLE 3. Distribution of Minor Histopathologic Features in Punch Biopsies and Excisions in DE Group and RCM Group

	DE (42 Cases)		RCM (30 Cases)	
Minor Histologic Features	**Biopsy (%)**	**Excision (%)**	**Biopsy (%)**	**Excision (%)**
Epidermal atrophy	28 (66.7)	28 (66.7)	16 (53.3)	20 (66.7)
Epidermal hypertrophy	14 (33.3)	14 (33.3)	14 (46.7)	10 (33.3)
Basal keratinocytes hyperpigmentation	31 (73.8)	35 (83.3)	22 (73.3)	21 (70.0)
Melanophages in papillary derma	37 (88.1)	34 (80.9)	22 (73.3)	15 (50.0)
Dermal inflammatory infiltrate	20 (47.6)	21 (50.0)	20 (66.7)	13 (43.3)
Solar elastosis	40 (95.2)	42 (100)	30 (100)	30 (100)

P, not significant.

TABLE 4. Number of Major Histopathologic Criteria in Punch Biopsies DE and RCM Guided

No. of Criteria	DE (%)	RCM (%)
0	0 (0)	1 (3.0)*
1	0 (0)	1 (3.0)
2	7 (17.0)	2 (7.0)
3	11 (26.0)	4 (13.0)
4	9 (21.0)	9 (30.0)
5	15 (36.0)	13 (44.0)
Total cases	42 (100)	30 (100)

*One case of desmoplastic melanoma without junctional melanocytes, $P = 0.005$.

Pigmented macules on the face are particularly challenging for clinicians, given the possible coexistence of different lesions in the same field. In fact, lesions contiguous to LM, represented mainly by solar lentigo, actinic keratosis, and seborrheic keratosis, have been found in 48% of facial LM cases in one study, contributing to the risk of sampling error.[18] In our study, we observed nonmelanocytic or benign lesions associated with LM/LMM in quite a high percentage of cases, both in punch biopsies and, even more, in excisional specimens, as expected given the larger dimension of the specimens.

In this study, 2 small lesions, that is, one case of LM evaluated with DE, and one LMM evaluated with RCM, resulted completely excised with biopsy. This finding would suggest the concept of "vanishing melanoma," similar to the well-known phenomenon of "vanishing carcinoma," described in prostate[19] and endometrial cancer.[20] As for other organs, it is important to underline the possibility of removing the entire LM/LMM with a small biopsy, particularly on sun-damaged skin, where a melanoma can easily coexist with other pigmented lesions. In fact, in the 2 cases of "vanishing melanoma" in our series, a solar lentigo was observed in surgical excision.

In contrast to the results of the previous study at naked eye,[5] our study demonstrated that DE and RCM provide overall a higher percentage of concordant diagnosis between biopsy and excision, a lower percentage of cases with more histopathologic criteria in the excisional sample than in punch biopsy, and a lower percentage of infiltrating melanomas in the excisional sample when only an in situ lesion was visible in biopsy. Importantly, false-positive cases were not registered in our study, and therefore, inappropriate surgical treatment was avoided.

TABLE 5. Comparison of the Number of Major Criteria in Punch Biopsies and Excisions Between DE Group and RCM Group

	DE (%)	RCM (%)
More criteria in biopsy than excision	7 (16.7)	7 (23.3)
Same no. of criteria		
In biopsy and excision	20 (47.6)	17 (56.7)
More criteria in		
Excision than biopsy	15 (35.7)	6 (20.0)
Total cases	42 (100)	30 (100)

$P = 0.04$.

TABLE 6. Comparison of Results in Somach's Study and in Present Study

	Somach's Study (46 Cases)	Present Study (72 Cases)
Excision did not show more specific criteria for LM/LMM as compared to biopsy	25 (54%) (2 cases of LMM at biopsy with LM only at excision)	48 (67%) (1 LM and 1 LMM at biopsy; lesions "vanishing" at excision)
More consistent features observed at excision as compared to biopsy; no dermal invasion	9 (20%)	8 (11%)
Biopsy showed only LM; excision showed an infiltrating melanoma	9 (20%)	6 (8%)
Biopsy and excision both showed an infiltrating melanoma	3 (7%)	10 (14%)

$P = 0.01$.

Because histopathology had always represented the gold standard for the final diagnosis of melanoma, we can reasonably affirm that a long-lasting and profitable collaboration between clinicians and pathologists has fostered the building of refined dermoscopic and confocal criteria to achieve, in skillful hands, high diagnostic level in approaching pigmented lesions on sun-damaged skin. With the limitation due to the not particularly high number of cases investigated, our study indicates that the evolution of these techniques now allows pathologists to handle specimens showing histopathologic features more consistent with LM/LMM, thus simplifying the diagnosis, and crucially, assuring a more accurate staging of tumor before surgery, and the optimal treatment of the patient.

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