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Dermoscopic Differentiation of Facial Lentigo Maligna from Pigmented Actinic Keratosis and Solar Lentigines

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ABSTRACT The differential diagnosis of lentigo maligna (LM) from pigmented actinic keratosis (PAK) and solar lentigines (SL) remains a challenge for clinicians, especially in the early stages of LM when there are no distinctive dermoscopic features. Objective of this study was to evaluate the frequencies of selective dermoscopic criteria in LM, PAK, and SL and to find the specific combination of distinguishing dermoscopic criteria for LM. Dermoscopists blinded to histopathological diagnosis evaluated 42 LM, 107 PAK, and 16 SL for the presence of predefined dermoscopic criteria. The differences in the presence of dermoscopic criteria between LM and others were evaluated with the chi-squared test or Fisher's exact test as appropriate. Multivariate logistic regression analysis with the forward conditional stepwise method were performed and odds ratios and corresponding 95% confidence intervals for LM, PAK, and SL were calculated. LM, PAK, and SL showed many common dermoscopic findings. In multivariate logistic regression analysis, darkening at dermoscopic examination (sevenfold), gray circles (sevenfold), target-like pattern (sixfold), gray rhomboids (sixfold), and slate-gray dots/globules (threefold) represented the strongest predictors of LM, while hyperkeratosis (thirteenfold), white circles (twelvefold), and red rhomboids (sixfold) represented the strongest predictors of PAK. The dermoscopic diagnosis of a given lesion should be based on the presence of the combination of specific dermoscopic criteria rather than a single benign or malignant criterion. Our results suggest that the presence of darkening at dermoscopic examination, gray circles, target-like pattern, gray rhomboids, and slate-gray dots/globules should be considered supportive findings for the diagnosis of early LM.

KEY WORDS: lentigo maligna, pigmented actinic keratosis, solar lentigines, dermoscopy

INTRODUCTION

The differential diagnosis of lentigo maligna (LM) on the face remains one of the most challenging conditions for clinicians. Although its incidence is gradually increasing because of higher cumulative exposure to ultraviolet radiation in recent years, delayed diagnosis is still common. Due to their similar appearance as flat pigmented lesions typically developing on sun-damaged skin of elderly individuals, clinical characteristics can be insufficient to allow the differentiation of early LM from solar lentigines (SL/early seborrheic keratoses) and pigmented actinic keratosis (PAK). However, an accurate diagnosis is essential, as melanoma shows significant differences in biologic behavior, prognosis, and treatment (1,2).

Dermoscopy has become an integral part of the clinical examination of skin tumors by improving diagnostic accuracy compared with the naked eye (1). The important dermoscopic findings for early recognition of LM were first described by Schiffner *et al*., and then a four-step progression model for LM was proposed. Asymmetric pigmented follicular openings, annular granular pattern, rhomboidal structures, and

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obliterated hair follicles represent the main progression steps in this model (3,4). In the following years, novel dermoscopic features were described by other researchers, such as darkening at dermoscopic examination, a target-like pattern, red rhomboids, and increased density of the vascular network (5). Of course, establishing a definite diagnosis is usually not difficult when the lesion already exhibits those fully developed specific dermoscopic criteria. However, at earlier stages, dermoscopic differentiation of LM from a picture of PAK or an irregular pigmented SL remains complicated even for highly experienced dermatologists (1,2,5).

In the present study, we aimed to evaluate the frequencies of selective dermoscopic criteria in LM, PAK, and SL; to find the specific combination of distinguishing dermoscopic criteria for LM; and to build a scoring scheme for the diagnosis of LM based on the results obtained.

PATIENTS AND METHODS

Data collection

The database of our dermoscopy unit was screened to identify eligible facial pigmented flat lesions which underwent biopsy for histopathological confirmation in order to rule out LM. Inclusion criteria were a definite histopathological diagnosis of LM, PAK, or SL, Breslow thickness < 1 mm for invasive LM, and the availability of high-quality dermoscopic images showing at least two thirds of the lesion surface. For each patient, information on sex and age at the time of diagnosis was retrieved from the medical records. The specific anatomic location of the lesions was determined from the clinical image archive of the dermoscopy unit. The Breslow thickness and Clark level of the invasive LMs were retrieved from the histopathological records.

Data regarding these lesions were collected between January 2004 and May 2017 at the Dermoscopy Unit of the Dokuz Eylul University, Faculty of Medicine in Izmir, Turkey. All dermoscopic images included in the study were collected with a non-polarized contact digital dermoscope (Mole Max II, Derma Instruments, Vienna, Austria) at 30 or 40-fold magnification using 70% ethanol handwash gel.

Two dermatologists highly experienced in dermoscopy (O.O. and S.A.) evaluated the dermoscopic images blinded to histopathological diagnoses, and were asked to evaluate the presence or absence of the predefined criteria. The selection of these dermoscopic criteria in the study was based on previously described features of LM, PAK, and SL in the dermoscopic literature. When no consensus could be reached among the two investigators, the criterion was discussed with a third investigator (E.F.).

Ethics

The study protocol was approved by the Local Ethics Committee which follows the guidelines set by the Helsinki declaration.

Statistical analysis

Dichotomous variables (yes/no) were recorded for each histopathological diagnosis, and the differences in the presence of dermoscopic features between LM and other lesions (both PAK and SL) were evaluated with the chi-squared test or Fisher's exact test as appropriate. Constant variables in the data set were expressed as mean ± standard deviation, and categorical variables were expressed as frequency and percentage. All separate dermoscopic variables were included in the analysis, and corresponding 95% confidence intervals were calculated by multivariate logistic regression analysis using the forward conditional stepwise method. The alpha level was set at 0.05, while an alpha level of 0.10 was used as a cut-off for variable removal in the automated model selection for multivariate logistic regression. All statistical calculations were performed with SPSS 22.0 (SPSS Inc., Chicago, IL, USA). A *P*-value <0.05 was regarded statistically significant.

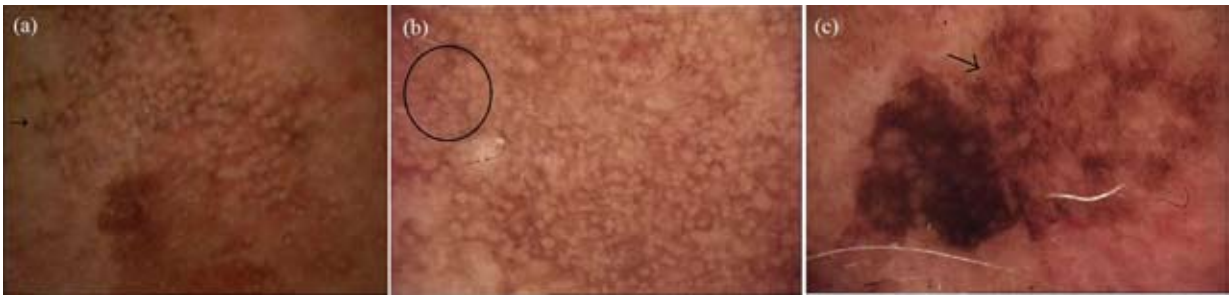

Figure 1. (a) Lentigo maligna displaying asymmetric pigmented follicular openings, brown and gray rhomboids, and target-like pattern (arrow). (b) Pigmented actinic keratosis displaying hyperkeratosis and white circles (circle). (c) Solar lentigo displaying finger-print like structures and irregular pigmentation with gray color.

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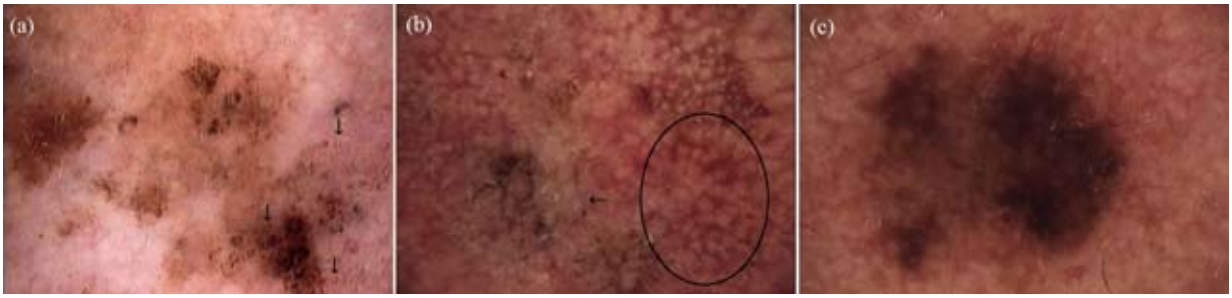

Figure 2. (a) Early invasive lentigo maligna (0.1 mm Breslow thickness) showing brown and gray colors and gray circles (arrows). (b) Pigmented actinic keratosis with prominent hyperkeratosis (arrow), red and gray rhomboids (circle). (c) Solar lentigo showing a prominent gray color and irregular pigmentation.

RESULTS

Demographic and clinical findings

A total of 165 flat pigmented facial lesions belonging to 42 (25.5%) LM (36 in situ, 6 invasive), 107 (64.8%) PAK, and 16 (9.7%) SL in 108 men and 57 women with age ranging from 42 to 89 (mean 67.02±11.62) were collected. The mean age of the patients was 65.74±11.11 years in women and 67.70±11.87 years in men (*P*=0.303). Whereas the male-to-female ratio

Table 1. The incidences of the dermoscopic criteria in our series

Dermoscopic criteria	LM (n = 42)	PAK (n = 107)	SL (n = 16)	p value
Colors				
Gray color	30 (71.4)	70 (65.4)	5 (31.3)	0.224
Red color	15 (35.7)	60 (56.1)	1 (6.3)	0.119
Patterns				
Asymmetric pigmented follicular openings	24 (57.1)	35 (32.7)	8 (50)	**0.011***
Annular granular pattern	23 (54.8)	43 (40.2)	5 (31.3)	0.075
Dark rhomboids	26 (61.9)	54 (50.5)	3 (18.8)	0.082
Obliteration of follicular openings	6 (14.3)	0	0	**<0.001***
Brown-black dots/globules	19 (45.2)	24 (22.4)	4 (25)	**0.005***
Slate-gray dots/globules	22 (52.4)	38 (35.5)	3 (18.8)	**0.028***
Gray circles	21 (50)	13 (12.1)	4 (25)	**<0.001***
White circles	2 (4.8)	50 (46.7)	1 (6.3)	**<0.001***
Circle in a circle	6 (14.3)	5 (4.7)	1 (6.3)	0.077
Target-like pattern	9 (21.4)	15 (14)	0	0.143
Inner gray halo	3 (7.1)	17 (15.9)	0	0.252
Gray rhomboids	22 (52.4)	25 (23.4)	1 (6.3)	**<0.001***
Red rhomboids	6 (14.3)	68 (63.6)	3 (18.8)	**<0.001***
Gray brown streaks	3 (7.1)	3 (2.8)	0	0.173
Dark streaks	9 (21.4)	6 (5.6)	0	**0.003***
Darkening at dermoscopic examination	12 (28.6)	10 (9.3)	0	**0.001***
Broken pseudonetwork	4 (9.5)	24 (22.4)	0	0.137
Hyperkeratosis	5 (11.9)	76 (71)	2 (12.5)	**<0.001***
Strawberry sign	4 (9.5)	32 (29.9)	0	**0.025***
Sharp demarcation	11 (26.2)	23 (21.5)	5 (31.3)	0.652
Milia-like cysts	3 (7.1)	12 (11.2)	2 (12.5)	0.564
Comedo-like openings	5 (11.9)	4 (3.7)	3 (18.8)	0.185
Fingerprint-like structures	14 (33.3)	16 (15)	6 (37.5)	**0.036***
Moth-eaten border	18 (42.9)	46 (43)	7 (43.8)	0.979
Jelly sign	6 (14.3)	10 (9.3)	4 (25)	0.619
Yellow opaque homogeneous areas	5 (11.9)	14 (13.1)	4 (25)	0.659

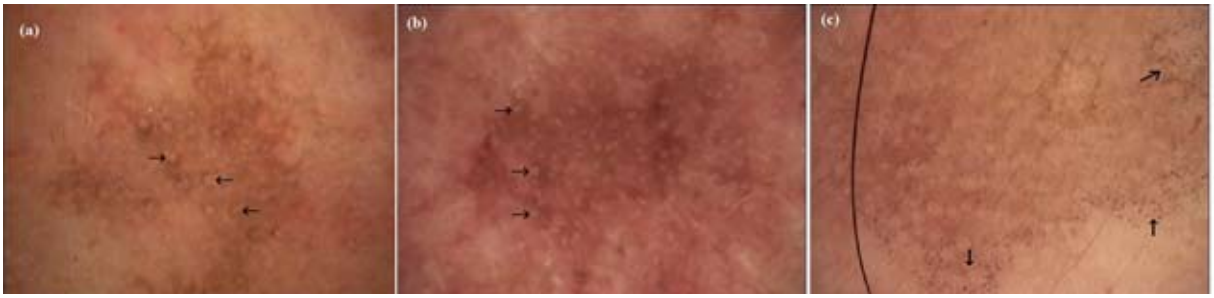

Figure 3. (a) A lightly pigmented lentigo maligna displaying gray color and asymmetric pigmented follicular openings (arrows). (b) Gray color in a lightly pigmented actinic keratosis showing background erythema, and white circles in the follicular openings (arrows). (c) Multiple slate-gray dots and globules (arrows) in a lightly pigmented solar lentigo.

did not differ in the LM and SL groups, there was a male preponderance in the PAK group (71% vs 29%, *P*=0.041). Included lesions were located on the malar areas (29.7%), the nose (28.5%), forehead (25.5%), zygomatic areas (13.3%), ears (1.8%), and chin (1.2%). No correlation was found between the location and the histopathological diagnosis. The Clark level was II and tumor thickness was <1 mm in all invasive LMs.

Frequencies and significances of dermoscopic findings

The distributions and incidences of the examined dermoscopic criteria in our LM, PAK, and SL series are shown in Table 1 and Figures 1-3. All lesions contained light and dark brown colors. Other than brown, gray was the most frequently observed color in LM (71.4%), whereas red color was much more frequent in PAK compared with LM (56.1% vs 35.7%). Gray and red colors were also detected in 5 (31.3%) and 1 (6.3%) of 16 SLs, respectively.

The most frequently observed dermoscopic feature in LM was dark rhomboids (61.9%), followed by asymmetric pigmented follicular openings (57.1%) and annular granular pattern (54.8%). In PAK, hyperkeratosis (71.0%), red rhomboids (63.6%), and dark rhomboids (50.5%) represented the most common dermoscopic findings. Asymmetric pigmented follicular openings (50%), moth-eaten border (43.8%), and fingerprint-like structures (37.5%) were the most common features of SL.

Table 2. Dermoscopic predictors of LM, PAK and SL in the multivariate regression analysis

Variable	Odds ratio	95% Confidence interval	p value
Multivariate for LM			
Darkening at dermoscopic examination	7.43	1.48—37.17	0.015
Gray circles	7.34	2.10—25.70	0.002
Target-like pattern	6.32	1.19—33.65	0.031
Gray rhomboids	6.29	1.87—21.10	0.003
Slate-gray dots/globules	3.94	1.12—13.83	0.033
White circles	0.05	0.01—0.54	0.013
Hyperkeratosis	0.14	0.04—0.52	0.004
Red rhomboids	0.14	0.04—0.57	0.006
Multivariate for PAK			
Hyperkeratosis	13.97	4.75—41.05	<0.001
White circles	12.90	2.82—58.97	0.001
Red rhomboids	6.86	2.41—19.53	<0.001
Gray circles	0.15	0.05—0.49	0.002
Multivariate for SL			
Red color	0.01	0.001—0.19	0.002
Gray rhomboids	0.04	0.003—0.58	0.018
Gray color	0.05	0.01—0.32	0.002
Hyperkeratosis	0.06	0.01—0.51	0.010
Dark rhomboids	0.12	0.02—0.82	0.031

LM, lentigo maligna; PAK, pigmented actinic keratosis; SL, solar lentigines.

Table 3. Scoring scheme for lentigo maligna based on dermoscopic predictors

Darkening at dermoscopic examination	+1
Gray circles	+1
Target-like pattern	+1
Gray rhomboids	+1
Slate-gray dots/globules	+1
White circles	-1
Hyperkeratosis	-1
Red rhomboids	-1
Total score in the sample	-3 to +5

A total score ≥1 is suggestive of lentigo maligna with a specificity of 75.4% and a sensitivity of 95.1%.

Overall, the incidences of asymmetric pigmented follicular openings, obliteration of follicular openings, brown-black dots/globules, slate-gray dots/globules, gray circles, gray rhomboids, dark streaks, and darkening at dermoscopic examination were found to be significantly higher; whereas the incidences of white circles, red rhomboids, hyperkeratosis, strawberry sign, and fingerprint-like structures were found to be significantly lower in LM compared with PAK and SL (Table 1). Among all dermoscopic criteria, only the incidence of obliteration of follicular openings showed a statistically significant difference between in situ (2.8%, in 1 of 36 lesions) and invasive (83.3%, in 5 of 6 lesions) LMs ($P<0.001$).

In multivariate analysis, certain dermoscopic criteria showed positive significant associations with LM and PAK, whereas no criteria showed a positive significant association with SL. The results of these models are presented in Table 2. After that, aiming to create a clinically applicable diagnostic tool, we built a scoring scheme for diagnosing LM (Table 3). We included all of the significant multivariate LM predictors in the scoring scheme by giving +1 point for the features that had a positive OR and -1 point for the features that had a negative OR for LM. A total score ≥1 was found suggestive of LM with a specificity of 75.4% and a sensitivity of 95.1%, and the diagnostic accuracy of this score expressed as area under the receiver operating characteristics curve was 0.92 (95% CI: 0.88-0.96).

DISCUSSION

This study has confirmed that all of the dermoscopic features observed in the early stages of LM can also be observed in both PAK and SL, thus the differential diagnosis should be based on the presence of the combination of specific dermoscopic criteria. Although it is already well known that PAK is a great imitator of LM (6,7), the distinction between SL and LM may also be rather challenging in some cases. To date, only a few studies specifically examined the distinctive role of dermoscopic features between LM, PAK, and SL on the face (7-9). Considering the improving knowledge on diagnostic dermoscopy criteria in recent years, our study provides a comprehensive analysis of the distinctive roles of classical and novel dermoscopic features of these different entities.

Positive predictors of LM in multivariate analysis

Darkening at dermoscopic examination. This feature refers to the fact that the color seen through dermoscope is darker than in naked-eye examination. It was first described in a study by Pralong *et al*., in which the dermoscopic features of 125 LMs were examined. The researchers observed this feature in 25% of the invasive LMs and in 30% of the in situ LMs in their study (5). Although this feature was also uncommon in LMs in our study (28.6%), it represented the strongest predictor in the multivariate analysis in our sample.

Gray circles. In previous studies, gray circles were reported to show a high association with early LM, and this association even led to the hypothesis that LM may arise from cancer stem cells of the hair bulge rather than from transformed epidermal melanocytes (6,8). Understanding the fact that the appearance of follicular openings may be a useful in recognizing early LM, pigmentation and structures in the follicular openings have become the focus in recent studies. In a study by Tschandl *et al*., gray circles were found to show a high association with LM as opposed to PAK (10). In another study, Lallas *et al*. concluded that gray circles should be considered among the most significant predictors of LM (8). Our results have also confirmed that gray circles should be considered a valuable distinctive feature for the diagnosis of early LM.

Target-like pattern. This feature describes the presence of a dark dot in the center of the dark circle of a hyperpigmented hair follicle. Pralong *et al*. observed this feature in 36% of the in situ LMs in their study, and it was noted that this pattern may correspond to a specific form of pilar infundibulum invasion (5). In a recent study, Carbone *et al*. found the target-like pattern in 26% of the LMs and in 20% of the benign lesions in their study (9). In our study, this feature was detected in 21.5% of LMs and in 14% of PAKs. Although its incidence in LM did not even reach statistical significance in the chi-squared test in our study, the multivariate analysis demonstrated that this feature is an important clue in the diagnosis of early LM.

Gray rhomboids. Lallas *et al*. reported that gray rhomboids were found to be the most common feature associated with LM in their study (8). More-

over, previous publications have mentioned that the presence of any gray color in dermoscopic examination should be considered as an indicator of malignancy (10,11). Zivkovic *et al*. reported that the gray color is the single most sensitive feature for the dermoscopic recognition of early facial melanoma, as the gray color can be detected even before the formation of the characteristic LM structures, such as gray circles or gray rhomboids (11). On the contrary, recent studies have shown that both PAK and SL may also demonstrate this feature, stating that gray color alone has no distinguishing value between benign and malignant entities (7,8). This seems reasonable for PAK because of the location of melanin in macrophages of the dermis, and their appearance in gray color in dermoscopic examination would be similar to those seen in LM (2). However, melanin is exclusively found at the epidermal level (pigmented keratinocytes) in SL, and these lesions should theoretically display only brown color through the dermoscope. In contrast, Lallas *et al*. found the presence of gray color in about half of their SL lesions (8). Although gray color has been found to show a significant negative association with SL in multivariate analysis, we also detected the presence of gray color in some SLs in our study. However, due to the fact that it is not a necessary to perform histopathological examination in ordinary SLs which are easily diagnosed by clinical or dermoscopic examination, the SLs included in this study all consisted of compelling lesions showing common dermoscopic features with LM, such as the gray color. These results indicate that the dermoscopic diagnosis of a given lesion must not be based on the presence of only a single criterion, and the presence of the gray color in dermoscopic examination of the flat pigmented facial lesions should be considered highly suggestive of LM in the presence of other specific gray structures, such as gray rhomboids or gray circles.

Slate-gray dots/globules. Slate-gray dots, which can increase to globules, are among the previously described main four features of LM with asymmetric pigmented follicular openings and dark rhomboids (3,12). They reflect the clusters of melanophages in the upper dermis whose distribution around the follicular openings create an annular-granular pattern. However, slate-gray dots/globules may also be found in PAK, which histopathologically correlate with individually hyperpigmented keratinocytes in the Malpighian layer and aggregates of melanin-loaded macrophages located in the upper dermis. Akay *et al*. found that the incidences of slate gray dots and globules were higher in PAK compared with LM (6). On the other hand, Nascimento at al. found that they were more common in LM, which is also in accordance with our results (13). Slate-gray dots/globules in PAK can be dermoscopically differentiated from LM in most cases by the more regular architecture and the distribution of dots within the lesion (2). Our results have substantially confirmed that slate-gray dots/globules generally were of uniform size, and the distribution was homogeneous in 86% of PAKs in our study. However, in LMS we observed that they varied in size and had a tendency towards localization at the peripheral areas of the lesions. This form of granularity was usually linked to the diagnosis of melanoma on extrafacial skin in previous reports (14-16). We found this feature in 52.4% of facial LMs in our study, suggesting that this distribution of slate-gray dots/globules may also be an important clue for facial LMs.

Negative predictors of LM in multivariate analysis

White circles. This white ring-like structure within the hair follicle also correspond to the "rosettes" or "four dots in a square" when the lesion is viewed under polarized dermoscopy (8,10). Lallas *et al*. observed the white circles in 64% of PAK lesions in their study, and they found that white circles were the strongest predictor of PAK in comparison with LM (8). Although the incidence of white circles was lower in our PAK lesions (46.7%), they represented a strong negative predictor of LM in comparison with PAK in multivariate analysis.

Hyperkeratosis. In the study of Tschandl *et al*., hyperkeratosis was found to have the highest positive predictive value (72.2%), and a high specificity rate (94.2%) for PAK (10). Similarly, multivariate analysis for LM and PAK in Lallas *et al*. showed that the detection of scales on dermoscopy strongly favors the diagnosis of PAK (8). Consistently with such previous reports, our results also showed that the detection of hyperkeratosis on dermoscopic examination is the strongest predictor of PAK, having a nearly 14-fold increased probability in comparison with LM and SL (6,8,10,13).

Red rhomboids. In addition to their predictive value for PAK, red rhomboids are also among the recently described additional features of LM (5). However, their presence in LM is usually related with an increase in the vascular network, which is usually linked to the development of tumor-induced neovascularization in the advanced stages of the lesion (2,5,11). Pralong *et al*. showed that presence of red rhomboids in LM was significantly associated with invasion (5). The statistical significance of red rhomboids in PAK in comparison with LM in our study may be explained by the fact that this study included only early LMs.

Our study has some limitations which have to be pointed out. First, this was a retrospective study and the risk of recall and observation bias cannot be

absolutely ignored, although we tried to eliminate this risk by employing two independent blind investigators to examine the lesions and by referring to a third investigator if necessary. Second, the dermoscopic images in the study were obtained with only a non-polarized dermoscopic camera, which did not allow us to investigate the usefulness of criteria seen only under polarized light. Third, we were not able to visualize and analyze the distinctive role of the vascular structures in the majority of the images because of their compression due to the contact nature of our dermoscopy device, and thus no conclusions can be drawn from our study on this issue.

CONCLUSION

Our results have confirmed that the presence of darkening at dermoscopic examination, gray circles, target-like pattern, gray rhomboids, and slate-gray dots/globules should be considered supportive findings for the diagnosis of early LM, while the presence of white circles, hyperkeratosis, and red rhomboids should be considered as indicative of PAK. This study has also demonstrated that many of the criteria described for facial LM are not unique to facial LM and can be commonly seen in PAK and SL. When examining a facial lesion, it is imperative that the dermoscopic diagnosis of the lesion not be based on the presence of a single benign or malign criterion. The entire lesion must be evaluated dermoscopically, and the overall pattern of the lesion and the association of different dermoscopic criteria should be considered. Nonetheless, as the most important risk for clinicians evaluating a facial pigmented lesion is to miss the diagnosis of a LM, it should be kept in mind that a histopathologic examination should be performed whenever the dermoscopic results lead to ambiguity.

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