Dermatoscopy of nodular/plaque-type primary cutaneous T- and B-cell lymphomas: A retrospective comparative study with pseudolymphomas and tumoral/inflammatory mimickers by the International Dermoscopy Society

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Background: Limited data on dermatoscopy of nodular/plaque-type T-/B-cell primary cutaneous lymphomas (PCLs) is available.

Objective: To describe dermatoscopic features of nodular/plaque-type PCLs, comparing them with those of clinical mimickers (pseudolymphomas, tumors, and inflammatory lesions) and investigating possible differences according to histologic subtypes.

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Methods: Participants were invited to join this retrospective, multicenter case-control study by submitting histologically/immunohistochemically confirmed instances of nodular/plaque-type PCLs and controls. Standardized assessments of the dermatoscopic images and comparative analyses were performed.

Results: A total of 261 lesions were included (121 PCLs and 140 controls). Orange structureless areas were the strongest PCL dermatoscopic predictor on multivariate analysis compared with tumors and non-infiltrative inflammatory dermatoses. On the other hand, a positive association was found between PCLs and either unfocused linear vessels with branches or focal white structureless areas compared with infiltrative inflammatory dermatoses, whereas white lines were predictive of PCLs over pseudolymphomas. Differences in the vascular pattern were also seen between B- and T-cell PCLs and among B-cell PCL subtypes.

Limitations: Retrospective design and the lack of a dermatoscopic-pathologic correlation analysis.

Conclusion: Nodular/plaque-type PCLs display dermatoscopic clues, which may partially vary according to histologic subtype and whose diagnostic relevance depends on the considered clinical differential diagnoses. (J Am Acad Dermatol 2022;86:774-81.)

Key words: dermatoscopy; infiltrative dermatoses; inflammatory dermatoses; lymphomas; pseudolymphomas; tumors.

INTRODUCTION

Primary cutaneous lymphomas (PCLs) are a heterogeneous group of T- and B-cell lymphomas localized on the skin, with no evidence of extracutaneous involvement at the time of diagnosis.[1,2] Except for mycosis fungoides and lymphomatoid papulosis, which display peculiar morphologic patterns, most types of PCLs manifest as nonspecific, reddish-purple nodules or plaques, with a consequent wide list of possible differential diagnoses that includes tumoral and inflammatory conditions.[1-3] The most common forms of nodular/plaque-type T-cell PCLs are $CD30^+$ anaplastic large cell lymphoma and $CD4^+$ small/medium lymphoproliferative disorder, whereas marginal zone lymphoma and follicle-center cell lymphoma represent the most frequent variants of nodular/plaque-type B-cell PCLs.[1,2]

Although the definitive diagnosis relies on histologic and immunohistochemical analyses, growing evidence supports a possible role of dermatoscopy in increasing the index of suspicion for PCLs besides clinical/anamnestic data.[4-12] However, while dermatoscopic features of mycosis fungoides have been investigated by several case-control studies, data on cutaneous lymphomas manifesting as nodules and/or plaques are scarce, with few case reports/series and only 1 small case-control study published in the literature.[12] Additionally, little information is available on possible dermatoscopic differences among PCLs and on the usefulness of dermatoscopy for the differential diagnosis between nodular/plaque-type PCLs and either pseudolymphomas or clinically similar inflammatory lesions.[12]

CAPSULE SUMMARY

- Our study increases the knowledge on dermatoscopy of nodular/plaque-type cutaneous lymphomas by comparing their dermatoscopic features with those of clinical mimickers and investigating possible differences according to histologic background.
- Significance of dermatoscopic findings in nodular/plaque-type cutaneous lymphomas should be interpreted based on the considered differential diagnosis and histologic subtype.

The aims of this study were to investigate the dermatoscopic morphology of different PCL subtypes manifesting as nodules or plaques and to assess the value of dermatoscopic criteria for the discrimination of PCLs from clinical mimickers (including pseudolymphomas, tumors, and inflammatory lesions). The study was conducted in accordance with ethical guidelines, and institutional review board approval was obtained from the Institutional Review Board (IRB-DAME) of University of Udine, Italy.

METHODS

This was a retrospective case-control study that was part of a larger project on PCLs launched by the International Dermoscopy Society via an online

Abbreviations used:

CI: confidence interval
OR: odds ratio
PCL: primary cutaneous lymphoma

call published on their website; (www.dermoscopy-ids.org).

PCLs diagnosed by histologic and immunohistochemical analyses clinically manifesting as single/multiple nodules or plaques were eligible for the current analysis (in case of multiple lesions in a single patient, we considered only the target lesion that was biopsied). Lymphomatous conditions presenting with either different clinical morphologies (ie, lymphomatoid papulosis and mycosis fungoides, typically characterized by papules and scaly patches/plaques, respectively) or extracutaneous manifestations (ie, leukemia cutis and systemic lymphomas with secondary cutaneous involvement) were, therefore, excluded from the study. Additionally, patients currently or previously treated were also not included to avoid biases resulting from possible modifications of dermatoscopic patterns by therapies.

The control group consisted of nodular/plaque-type skin lesions for which PCL was included in the clinical differential diagnosis at the time of initial presentation; only untreated and histologically confirmed lesions were considered eligible (immunohistochemistry and molecular analyses were also required for pseudolymphoma diagnosis).

High-quality clinical and dermatoscopic pictures (captured at ×10 magnification) and information on each patient's age and gender, target lesion localization, and histological subtype (for PCL group) were mandatory.

Two independent investigators (EE, AL), blinded to the clinical presentation and final diagnosis, evaluated the images for the presence of predefined dermatoscopic criteria. Interobserver agreement was evaluated through Cohen kappa coefficient. Dermatoscopic variables were selected according to the recent consensus document by the International Dermoscopy Society on dermatoscopy of infiltrative, infectious, and inflammatory dermatoses, which includes 5 standardized basic parameters with several possible subitems for each of them: (1) vessels (morphology and distribution); (2) scales (color and distribution); (3) appendage findings; (4) "other structures" (features other than vessels, scales, and follicular findings) (including color and morphology); and (5) "specific clues" (features strongly suggestive of a dermatosis due to a strict correlation with highly specific/sensitive histologic findings).[13]

Statistical analysis

All separate clinical and dermatoscopic variables were included in the analysis. Categorical data are presented as numbers and frequencies and were compared using the Pearson chi-square test. Relative risks were calculated for all dichotomous variables. Crude and adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated using univariate and conditional multivariate logistic regression, respectively. Forward inclusion and backward elimination were used. The α level was set at 0.05, and an α level of 0.20 was used as the cutoff for variable removal in the automated model selection for multivariate logistic regression. Variables that were statistically significantly associated with diagnoses were also controlled via multivariate logistic regression. Because a large number of predictors were to be included in the univariate analyses, we employed the Bonferroni correction for multiple hypothesis testing (setting $P < .001$ for 10 to 30 variables). The type I error probability associated with all tests in this study was set to 0.05. Statistical analyses were performed using the statistical package for social sciences statistical software (version 24.0, IBM SPSS Statistics for Windows, IBM Corp).

RESULTS

A total of 261 lesions provided by 16 different centers were recruited for the analysis. These included 95 B-cell PCLs (44 marginal zone lymphomas, 37 follicle-center cell lymphomas, and 14 diffuse large cell B-lymphomas) and 26 T-cell PCLs (17 $CD30^+$ anaplastic large cell lymphomas and 9 $CD4^+$ small/medium lymphoproliferative disorders) in the lymphomas group (total cases: 121). Included in the control group were 33 pseudolymphomas, 56 tumors (17 basal cell carcinomas, 9 squamous cell carcinomas, 8 adnexal tumors, 4 Merkel cell carcinomas, 3 dermatofibrosarcoma protuberans, 3 seborrheic keratoses, 3 metastases, 2 amelanotic melanomas, 2 cellular dermatofibromas, 2 leiomyomas, 1 dermal nevus, 1 atypical Spitz tumor, and 1 Kaposi sarcoma), 29 infiltrative inflammatory dermatoses (21 granulomatous dermatoses and 8 histiocytoses), and 22 noninfiltrative inflammatory dermatoses (8 discoid lupus erythematosus, 6 granuloma faciale, 2 lupus tumidus, 2 persistent insect bites, 2 epidermoid cysts, 1 molluscum contagiosum, and 1 hypertrophic lichen planus) (total cases: 140).

Details on analytic results and comparative analyses of dermatoscopic findings for cases and controls (as a whole and divided into clinical subtypes)

Table I. Dermatoscopic comparative analysis between nodular/plaque-type T- and B-cell primary cutaneous lymphomas and control subgroups (neoplastic lesions, infiltrative inflammatory dermatoses, noninfiltrative dermatoses, and pseudolymphomas) with prevalence data and statistical differences

Dermatoscopic variable	Lymphomas (N = 121) n (%)	Neoplastic lesions (N = 56) n (%)	Infiltrative dermatoses (N = 29) n (%)	Noninfiltrative dermatoses (N = 22) n (%)	Pseudolymphomas (N = 33) n (%)	*P* value*
Dotted vessels (unfocused)	34 (28.1)	8 (14.3)	4 (13.8)	5 (22.7)	9 (27.3)	-
Dotted vessels (with white halo)	0 (0.0)	**5 (8.9)**	0 (0.0)	0 (0.0)	0 (0.0)	.003†
Dotted vessels (unspecific distribution)	24 (19.8)	6 (10.7)	**1 (3.4)**	1 (4.5)	7 (21.2)	.048‡
Linear vessels (well-focused)	0 (0.0)	2 (3.6)	**3 (10.3)**	0 (0.0)	0 (0.0)	.007‡
Linear vessels (peripheral distribution)	3 (2.5)	4 (7.1)	1 (3.4)	**3 (13.6)**	**4 (12.1)**	.047§ .038‖
Linear vessels with branches (well-focused)	11 (9.1)	**18 (32.1)**	**12 (41.4)**	0 (0.0)	1 (3.0)	<.001† <.001‡
Linear vessels with branches (unfocused)	48 (39.7)	**10 (17.9)**	**3 (10.3)**	9 (40.9)	15 (45.5)	.006† .002‡
Linear-curved vessels (well-focused)	0 (0.0)	**3 (5.4)**	**3 (10.3)**	0 (0.0)	**2 (6.1)**	.031† .007‡ .045‖
Linear-curved vessels (unfocused)	35 (28.9)	14 (25.0)	**2 (6.9)**	6 (27.3)	4 (12.2)	.015‡
White structureless areas (total)	69 (57.0)	34 (60.7)	**7 (24.1)**	**4 (18.2)**	17 (51.5)	.002‡ .001§
White structureless areas (diffuse)	3 (2.5)	**9 (16.1)**	0 (0.0)	2 (9.1)	0 (0.0)	.002†
White structureless areas (focal)	66 (54.5)	25 (44.6)	**7 (24.1)**	**2 (9.1)**	17 (51.5)	.004‡ <.001§
Brown structureless areas (total)	1 (0.8)	**6 (10.7)**	0 (0.0)	1 (4.5)	1 (3.0)	.004†
Orange structureless areas (total)	73 (60.3)	**1 (1.8)**	22 (75.9)	**4 (18.2)**	16 (48.5)	<.001† <.001§
Orange structureless areas (focal)	66 (54.5)	**1 (1.8)**	15 (51.7)	**2 (9.1)**	12 (36.4)	<.001† <.001§
Yellow structureless areas (total)	0 (0.0)	**3 (5.4)**	**3 (10.3)**	0 (0.0)	0 (0.0)	.031† .007‡
Purple structureless areas (total)	3 (2.5)	**7 (12.5)**	**4 (13.8)**	0 (0.0)	0 (0.0)	.012† .026‡
Brown globules	0 (0.0)	**4 (7.1)**	0 (0.0)	0 (0.0)	1 (3.0)	.009†
Blue globules	0 (0.0)	**6 (10.7)**	0 (0.0)	0 (0.0)	0 (0.0)	.001†
Orange globules	8 (6.6)	0 (0.0)	1 (3.4)	0 (0.0)	1 (3.0)	-
White lines (total)	51 (42.1)	**14 (25.0)**	12 (41.4)	**3 (13.6)**	**7 (21.2)**	.030† .015§ .042‡
White lines (unspecifically arranged)	31 (25.6)	8 (14.3)	6 (20.7)	3 (13.6)	4 (12.1)	-

Bold text indicates statistically significant differences compared to lymphomas group.
*Pearson chi-squared test (statistical significance set at $P < .05$).
†Lymphomas versus neoplastic lesions.
‡Lymphomas versus infiltrative dermatoses.
§Lymphomas versus noninfiltrative dermatoses.
‖Lymphomas versus pseudolymphomas.

are shown in Table I and Supplementary Table I (available via Mendeley at https://doi.org/10.17632/j2xtp9k2jt.1). The interobserver agreement for dermatoscopic variables was high, with a Cohen kappa ranging from 0.67 to 0.91.

The main vascular findings of nodular/plaque-type PCLs turned out to be unfocused linear vessels with branches (39.7%), followed by unfocused dotted (28.9%) and linear-curved (28.1%) vessels, whereas focal white and orange structureless areas (54.5% for both) and white lines (total: 42.1%; unspecifically arranged: 25.6%) were the most common nonvascular features. Of note, all the aforementioned dermatoscopic findings, along with orange globules, were significantly more common in the PCL group compared to the control group. On

Table II. Multivariate (adjusted) dermatoscopic predictors for nodular/plaque-type T- and B-cell primary cutaneous lymphomas compared with the whole control group and different clinical subgroups (neoplastic lesions, infiltrative inflammatory dermatoses, noninfiltrative inflammatory dermatoses, and pseudolymphomas)

Dermatoscopic variable	*P* value*	Odds ratio†	Low 95% CI	High 95% CI
Lymphomas vs all controls				
Linear vessels with branches (well-focused)	.008	0.300	0.123	0.735
White structureless areas (focal)	.005	2.350	1.291	4.277
Orange structureless areas (focal)	<.001	3.957	2.132	7.342
Purple structureless areas (total)	.030	0.180	0.038	0.850
Orange globules	.033	6.618	1.170	37.437
White lines (total)	.044	1.935	1.017	3.682
Lymphomas vs neoplastic lesions				
Linear vessels with branches (well-focused)	.018	0.256	0.082	0.795
White structureless areas (diffuse)	.025	0.047	0.003	0.681
Brown structureless areas (total)	.028	0.083	0.009	0.760
Orange structureless areas (total)	<.001	65.011	6.860	616.101
Purple structureless areas (total)	.045	0.119	0.015	0.954
Lymphomas vs infiltrative inflammatory dermatoses				
Linear vessels with branches (unfocused)	.038	4.245	1.086	16.589
White structureless areas (total)	.004	9.473	2.034	44.118
Purple structureless areas (total)	.002	0.021	0.002	0.229
Lymphomas vs noninfiltrative inflammatory dermatoses				
White structureless areas (focal)	.003	10.103	2.156	47.339
Orange structureless areas (total)	.003	10.464	2.234	49.011
Lymphomas vs pseudolymphomas				
White lines (total)	.049	2.498	0.999	6.243

CI, Confidence interval.
*$P < .05$ deemed as statistically significant.
†Odds ratios approximated via multivariate logistic regression.

the other hand, well-focused vessels (linear, linear with branches, and linear-curved), dotted vessels with white halos, diffuse white structureless areas, brown and blue globules, and brown, purple, and yellow structureless areas were significantly more common in the controls. Nevertheless, only a few of the aforementioned criteria were found to represent robust diagnostic predictors in the univariate (Supplementary Table II available via Mendeley at https://doi.org/10.17632/j2xtp9k2jt.1) and multivariate analysis (Table II). In detail, the latter revealed a positive association between nodular/plaque-type PCLs and the following findings: focal white (OR 2.35; 95% CI 1.29 to 4.28) and orange (OR 3.96; 95% CI 2.13 to 7.34) structureless areas, orange globules (OR 6.62; 95% CI 1.17 to 37.44), and white lines (total) (OR 1.94; 95% CI 1.02 to 3.69) (Fig 1). Conversely, linear vessels with branches (well-focused) and purple structureless areas showed an inverse correlation (OR 0.30; 95% CI 0.12 to 0.74 and OR 0.18; 95% CI 0.04 to 0.85, respectively).

When it comes to the comparative subanalysis between PCLs and each subtype of controls, several significant differences were observed (Table I), with a variable correlation on univariate (Supplementary Table III available via Mendeley at https://doi.org/10.17632/j2xtp9k2jt.1) and multivariate (Table II) analyses. In particular, multivariate positive predictors of nodular/plaque-type PCLs included orange structureless areas (compared with tumors [OR 65.01; 95% CI 6.86 to 616.10] and noninfiltrative inflammatory dermatoses [OR 10.46; 95% CI 2.23 to 49.01]), focal white structureless areas (compared with infiltrative [OR 9.47; 95% CI 2.03 to 44.12] and noninfiltrative inflammatory dermatoses [OR 10.10; 95% CI 2.16 to 47.34]), unfocused linear vessels with branches (compared with infiltrative inflammatory dermatoses [OR 4.25; 95% CI 1.09 to 16.59]), and white lines (compared with pseudolymphomas [OR 2.50; 95% CI 0.99 to 6.24]) (Table II) (Supplementary Figs 1 and 2, available via Mendeley at https://doi.org/10.17632/j2xtp9k2jt.1). On the other hand, diffuse white structureless areas, brown structureless areas, and purple structureless areas turned out to be negatively associated with PCLs (all of them compared with tumors [OR 0.05, 0.08, and 0.12, respectively] and only the last one compared with infiltrative inflammatory dermatoses [OR 0.02]) (Table II) (Supplementary Fig 1).

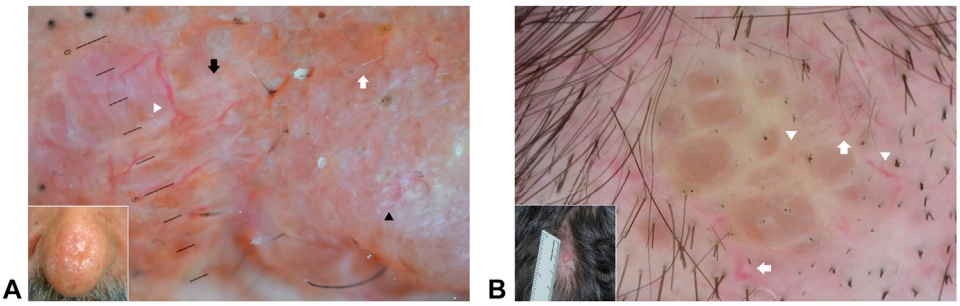

Fig 1. **A**, Marginal zone B-cell primary cutaneous lymphoma (PCL). Dermatoscopy reveals the main clues—white (*black arrow*) and orange (*white arrow*) structureless areas, unfocused vessels with branches (*white arrowhead*), and white lines (*black arrowhead*). **B**, Follicle-center B-cell PCL. Dermatoscopy shows orange globules along linear (*arrowheads*) and linear-curved (*arrows*) unfocused vessels.

The dermatoscopic analyses according to histologic PCL subtypes revealed only 1 potent predictor for the differential diagnosis between B-cell and T-cell PCLs: the presence of unfocused dotted vessels (Supplementary Table IV available via Mendeley at https://doi.org/10.17632/j2xtp9k2jt.1), which were significantly more common in T-cell PCLs (OR for B-cell PCLs: 0.31 [95% CI 0.12 to 0.79]) in the multivariate analysis (Supplementary Fig 2). Several differences were observed among B-cell PCL subtypes (Supplementary Table V available via Mendeley at https://doi.org/10.17632/j2xtp9k2jt.1), yet only the presence of unfocused linear vessels with branches was relevant on multivariate analysis, with an OR of 2.79 (95% CI 1.07 to 7.28) for marginal zone lymphoma (Supplemental Fig 2). Finally, no significant dermatoscopic difference was found among T-cell histologic subtypes (Supplementary Table VI available via Mendeley at https://doi.org/10.17632/j2xtp9k2jt.1).

DISCUSSION

In line with available literature data, the present analysis confirms that orange and white focal structureless areas are the most common nonvascular dermatoscopic findings of nodular/plaque-type PCLs (either B-cell or T-cell).[4-12] These features are supposed to correlate to the dense dermal cellular infiltrate ("mass effect") and either dermal reactive fibrosis or focally reduced "grenz zone" due to patchy, nodular, more superficial infiltrate in the papillary dermis, respectively.[8,11] Of note, the presence of orange color (either as globules or focal structureless areas) displayed the strongest positive association with nodular/plaque-type PCLs compared with the entire control group, consistent with previous data.[4-12] Additionally, white lines and focal white structureless areas were also positively linked to nodular/plaque-type PCLs, whereas purple structureless areas and well-focused linear vessels with branches showed a negative association. Indeed, vascular structures in nodular/plaque-type PCLs were mainly blurred, likely due to their location in the deeper dermis with consequent scattering of light by dermal collagen fibers, which may be increased in such lesions.[8,11,14] Interestingly, dermal fibrosis might also be responsible for the presence of white lines that turned out to be a relevant finding in our study.

Notably, compared to previous analyses, we observed a lower prevalence of follicular plugs and a different predominant vascular pattern, with linear vessels with branches being the most frequent.[4,5,8] It is possible that such differences are due to different sample size or different types of included lymphomas and variability of the lesions' duration, since the histologic background may vary according to a lesion's evolution stage.[11] However, the latter hypothesis has never been investigated so far due to the difficulty in assessing the precise onset of each nodule/plaque in multilesional instances.

We also compared dermatoscopic features of nodular/plaque-type PCLs to those of each clinical category of mimickers, highlighting several relevant differences. Indeed, whereas orange structureless areas turned out to be strongly associated with PCLs compared with tumors and noninfiltrative dermatoses, they were of no aid in distinguishing PCLs from infiltrative dermatoses and pseudolymphomas. This is because the latter entities are also histologically characterized by a dense cellular infiltrate, giving rise to an orange color on dermatoscopy.[15,16] However, according to our findings, unfocused linear vessels with branches and focal white structureless areas predicted the diagnosis of nodular/plaque-type PCLs compared with infiltrative dermatoses, whereas the

presence of white lines is predictive of nodular/plaque-type PCLs over pseudolymphomas. These differences are related to the histologic background, since infiltrative dermatoses, especially granulomatous dermatoses, are often typified by a dense cellular infiltrate that displaces the dermal vessels upward, so that they appear sharper on dermatoscopy (as they are closer to the skin surface).[15] On the other hand, the associations between nodular/plaque-type PCLs and both focal white areas and white lines might be due to the higher prevalence of reactive fibrosis compared to infiltrative dermatoses and pseudolymphomas.[11,13,17] Of note, this is the first study highlighting a possible dermatoscopic variability between PCLs and pseudolymphomas, as previous analyses assessed such conditions together, without comparing their dermatoscopic features.[8,12] The subgroup analysis between PCLs and other tumors also revealed 3 negative PCL predictors: white structureless areas (diffuse), purple structureless areas, and brown structureless areas, with the first 2 usually encountered in keratinizing tumors and the last 1 typical of pigment-producing lesions (of either melanocytic or nonmelanocytic derivation).

Finally, our analysis revealed variability in the dermatoscopic vascular pattern of PCLs according to their histologic subtype. Specifically, unfocused dotted vessels predicted T-cell over B-cell PCLs, while unfocused linear vessels with branches predicted marginal zone lymphomas over other B-cell PCL variants. No significant difference was found among T-cell PCL subtypes. It is possible that the observed variability in vascular morphology might be due to different patterns of angiogenesis, as it has been demonstrated that vessel growth in PCLs is influenced by tumor cell type as well as different microenvironments.[18,19]

The main limitation of the present study is its retrospective design, which is prone to recall and observation biases, which were addressed by involving evaluators who did not contribute to the sample collection. A large number of predictors were included in the univariate analyses without correction for multiple hypothesis testing. In fact, we chose to analyze each predictor separately, as several features were very likely to be statistically significant just by spurious association or chance given the number of independent tests that were performed. Additionally, the P value of each significantly flagged predictor is indicative of its value (with values $P < .001$ demonstrating those of importance), and those predictors that remained statistically significant in the multivariate analyses were already adjusted for the effect of other predictors and therefore could be deemed statistically significant. Finally, all mentioned dermatoscopic-pathologic correlations were based on previous studies or common reasoning, and the possible influence of lesion duration on dermatoscopic appearance was not considered. Consequently, our results should be interpreted with caution, and future research (including dermatoscopic-histologic analyses and analysis according to lesion stage) is needed to confirm our findings.

In conclusion, our findings emphasize that nodular/plaque-type PCLs may display several vascular and nonvascular clues on dermatoscopy, and the diagnostic significance of dermatoscopic criteria varies remarkably according to the clinical differential diagnosis. Additionally, some differences in terms of vascular dermatoscopic pattern may be observed among PCL subtypes. However, the decision to biopsy a specific lesion cannot rely only on dermatoscopic features but should be based on integrating anamnestic, clinical, and dermatoscopic findings, according to the "2-step" rule (clinical differential diagnosis followed by dermatoscopic examination).[16] On the other hand, dermatoscopy may guide clinicians in sampling the most informative lesion/area, as some dermatoscopic features are likely to be related to more relevant histologic findings (eg, orange areas and compact lymphomatous cellular infiltrate).

Conflict of interest

None disclosed.

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