

## Research Article

# Primary Cutaneous CD4+ Small/Medium T-Cell Lymphoproliferative Disorder (PCSM-LPD): Dermoscopic Clues to Address Its Diagnosis and Their Interobserver Reliability

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**Background:** Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (PCSM-LPD) is a rare lymphoid proliferation whose dermoscopic features are poorly defined, making diagnosis challenging. This study aims to identify the most common dermoscopic features of PCSM-LPD, assess their diagnostic accuracy, and evaluate interobserver reproducibility.

**Methods:** We conducted a retrospective study in a referral clinic, including patients with histologically confirmed PCSM-LPD and a control group of various cutaneous lymphomas. Two experienced dermatologists independently reviewed dermoscopic images. Key dermoscopic features were identified and compared between the groups. Interoperator reproducibility was measured using Cohen's Kappa. Diagnostic accuracy and agreement were the primary outcome measures.

**Results:** We analysed 18 PCSM-LPD cases and 18 controls. Serpentine vessels were the most common feature in PCSM-LPD, with a sensitivity of 100% and specificity of 76.5%. Keratin plugs had a sensitivity of 88.9% and a specificity of 77.8%. A yellow-orange background was also significant, with 100% sensitivity and 77.8% specificity. Interoperator agreement showed low to moderate Kappa values, with better agreement for vessel presence and keratin plugs but lower for vessel type and distribution.

**Discussion:** Serpentine vessels, keratin plugs, and yellow-orange background characteristics were found to be very sensitive and specific; however, their usability needs to be contextualised for diagnosing PCSM-LPD. Finally, despite high diagnostic accuracy, the interobserver agreement seems inconsistent, highlighting the need for standardised training. Further studies are necessary to validate these findings and improve diagnostic consistency in clinical practice.

**Keywords:** Cohen's Kappa; dermoscopy; diagnostic features; interoperator reliability; primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder

## 1. Introduction

Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (PCSM-LPD) is an infrequent and

distinct group of lymphoid neoplasms primarily affecting the skin [1–3]. It is a unique entity historically considered within the broader category of cutaneous T-cell lymphomas (CTCLs), even with a benign course, characterised by the

infiltration of malignant T-cells into the skin. PCSM-LPD specifically involves CD4+ T-lymphocytes, a subtype of T-cells expressing the CD4 cell surface marker [2–5].

The clinical presentation of PCSM-LPD varies among patients and may include solitary or multiple skin lesions, papules, nodules, or plaques [1]. However, the key to diagnosing PCSM-LPD lies in skin biopsies, which are crucial as they reveal the histopathological features and immunophenotypic profile of CD4+ T-cell involvement, confirming the disease [3].

Essential histological criteria for the diagnosis of PCSM-LPD are (a) a nodular and/or diffuse or a band-like infiltrate with a predominant CD4+ small or medium-sized pleomorphic T cells admixed with a B-cell component, (b) A T follicular Helper phenotype, characterised by a strong PD1 expression (by atypical cells) ± positivity for ICOS, BCL6, CXCL-13, but lack of CD10 expression. Among the desirable criteria, we consider adnexotropism, the absence of lymphoid follicles and the presence of scattered reactive cells, including CD8+ T cells, CD30+ cells, plasma cells, eosinophils, and histiocytes. The Ki-67 proliferation index should be low (around 25%), but up to 40% is acceptable in the proper clinical and histological context [6].

Surgical excision is the gold standard treatment for PCSM-LPD, although topical steroids and radiation therapy may be considered [7].

Dermoscopy is a method that can improve diagnostic accuracy in dermatology [8]. However, data on its use in the context of cutaneous lymphoid conditions are scarce [9, 10].

Only three more minor works have provided preliminary data on the dermoscopic characteristics of PCSM-LPD [8, 11, 12]. Based on these studies, dermoscopy of PCSM-LPD seems characterised by a lack of pigmentation and a vascular pattern with linear, irregular vessels with peripheral distribution and centripetal orientation, white-yellow comedo openings, and shiny white linear structures over a salmon-coloured homogenous background [12]. None of the available studies evaluated the sensitivity and specificity of these criteria, which may provide helpful clinical clues to diagnose this rare condition.

In conclusion, given its recent recognition as an independent entity in international classifications and its distinct histopathological and clinical profile, we considered it important to explore whether PCSM-LPD may also present specific and feasible dermoscopic features. Being able to identify such patterns could provide clinicians with helpful diagnostic clues and contribute to defining a reference framework for this rare and under-investigated condition. Moreover, as PCSM-LPD usually follows an indolent clinical course despite representing a T-cell clonal proliferation, the possibility of supporting its recognition through a non-invasive tool such as dermoscopy would be particularly valuable, potentially reducing the need for unnecessary biopsies and improving diagnostic confidence in routine practice.

Therefore, this study aims to test the criteria above regarding standard diagnostic accuracy measures (DAMs) and interobserver reproducibility.

## 2. Materials and Methods

To address the need for more information on the dermoscopic aspects, we undertook a comprehensive collection of all the cases referred to our centre. We systematically evaluated these cases to identify dermoscopic features that could be useful for a better and earlier diagnosis of these lesions [13, 14].

Once the visual and comparative characteristics have been collected, we wanted to evaluate them in a blind setting to determine their practical usability.

We retrospectively retrieved from our Cutaneous Lymphoma Unit dedicated database all confirmed PCSM-LPD cases after being reviewed histologically by two different experienced hematopathologists (C.A.; E.S.) and the same number of random samples of cases of cutaneous conditions considered a clinical differential diagnosis, such as mycosis fungoides, cutaneous marginal zone lymphoma, pseudolymphomas and cutaneous follicle centre lymphoma.

Once patient data had been registered, we also retrieved the clinical dermoscopy images of the lesion previously registered in our video-dermoscopy database. According to our internal standard operating procedure, all cutaneous lesions undergoing a skin biopsy have their clinical and dermoscopic image stored.

We retrospectively collected all PCSM-LPD cases followed by our unit and confirmed by histopathology and immunophenotyping in a specific database. Once patient data had been registered, we retrieved the specific clinical dermoscopy image of the lesion previously registered in our video-dermoscopy database for clinical and scientific purposes; this is the standard protocol for undergoing lesions that need anatomopathological analysis.

We then evaluated them by two experienced dermatologists trained in dermoscopy who treat cutaneous lymphomas (A.P., C.Z.). They analysed the digital images and had to describe all observable dermoscopic criteria.

For the control group, we retrospectively selected cases of cutaneous lymphoproliferative disorders that could represent clinical differential diagnoses of PCSM-LPD, including mycosis fungoides, cutaneous marginal zone lymphoma, pseudolymphomas and cutaneous follicle centre lymphoma. Controls were identified consecutively in reverse chronological order from the institutional video-dermoscopy database. This approach was used to reduce selection bias and ensure inclusion of all eligible histologically confirmed cases without preferential pre-selection. They were then collected in a 1:1 ratio to the PCSM-LPD cases, based on the availability of dermoscopic images taken before histological diagnosis and stored according to our standardised protocol. The ratio was adopted to preserve statistical symmetry in the calculation of DAMs and inter-rater agreement, while avoiding an excessive imbalance that could have further weakened the analysis given the heterogeneity of the control group.

Variables such as pigmentation, type of vessels, distribution of vessels, presence of keratin plugs, type of plugs, desquamation, distribution of desquamation, and background colour were evaluated. The class list of variables and

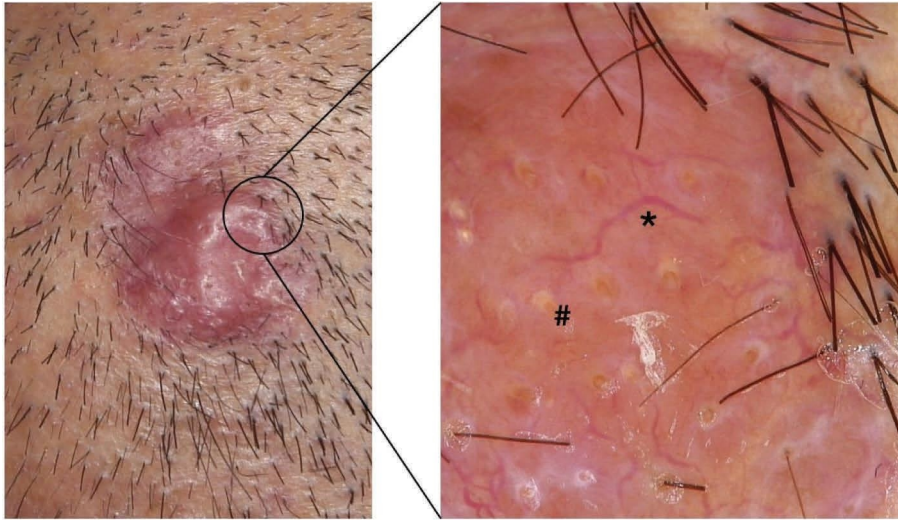


FIGURE 1: Dermoscopy of a PCSM-LPD and 40× magnification. Note the orange background, # the kerating plugs and \* the serpentine vessels.

terminology used was the one proposed by the International Dermatology Society consensus for dermoscopic oncological manifestations [15, 16] (Figure 1).

Then, the theoretical sensitivity and specificity for the most representative parameters of the collected dermoscopic features were calculated for the two groups using the known formulas [15] and the chi-square test to evaluate the significance.

Finally, the interobserver reproducibility of the proposed criteria was tested in a double-blinded randomised assessment by three unrelated and unfamiliar to the collected image operators experienced in dermoscopy with more than 5 years of dermoscopic training. Again, according to the IDS nomenclature, the reported characteristics were shown using the interoperator concordance coefficient, Choen's K.

All calculations were performed using SPSS IBM 26 and the charts were produced using python ver 3.3 (Code available [16] in <https://jupyter.org/>).

### 3. Results

**3.1. Clinical Data.** We retrieved 18 PCSM-LPD cases. The control group comprised 11 cases of mycosis fungoides (including patches, plaques and nodules), 4 type B cutaneous lymphomas, 2 centrofollicular and one CD30+ disorder. The distribution of anatomical sites and lesion morphology (classified as flat lesions such as patches vs. raised lesions such as papules, plaques or nodules) between the two groups did not show statistically significant differences ( $p > 0.05$ , chi-square test), supporting a reasonable degree of comparability.

**3.2. Frequencies Analysis.** All the dermoscopic variables analysed have been reported in (Table 1) (Figure 1).

We did not observe any pigmentation feature in any of the analysed images. Hence, we could not perform further analysis with these parameters.

Regarding vascularisation, the two groups showed clear dermoscopic signs of vascularisation except in one case in the control group (chi-square value: 3.27,  $p$  value: 0.195).

Looking more in detail at the types of vessels, we observed serpentine vessels in all 18 PCSM-LPD cases. In the control group, we observed serpentine vessels in 4 instances, dotted vessels in 5, linear in 4, clods in 2, coiled in 1 and glomerular in 1. Serpentine vessels were significantly more common in the PCSM-LPD group (chi-square value: 21.90,  $p$  value  $< 0.001$ ).

Subsequently, we analysed the vessels' distribution. In the PCSM-LPD group, we observed 9 cases with a branched pattern: 3 clustered, 3 radial and 3 serpiginous; in the control group, 3 branched, 2 clustered, 8 radial and 4 serpiginous.

The differences in the frequency distributions among groups and within each group were not statistically significant (chi-square value: 5.59,  $p$  value: 0.133).

In the PCSM-LPD group, 16/18 cases had keratin plugs but only in 4/18 in the control (chi-square value: 23.20,  $p$  value  $< 0.0001$ ).

Analysing the background colour, all the PCSM-LPD cases showed a yellow-orange background, while in the control group, 13 cases had a red, 4 a yellow-orange, and only 1 orange colour (chi-square value: 22.91,  $p$  value:  $< 0.0001$ ).

Finally, we did recognise some degree of desquamation in 4 cases of the PCSM-LPD group and 11 cases of the control group (chi-square value: 0.52,  $p$  value: 0.469), with a diffuse distribution in the PCSM-LPD group in 2 cases and central (1 case), diffuse (4 cases) and peripheric (1 case) (chi-square value: 0.89,  $p$  value: 0.641).

**3.2.1. DAMs.** Figure 2 looks at the DAMs for the parameters that showed significant differences between the PCSM-LPD and control group.

"Serpentine" type vessels are associated with a sensitivity of 100% in diagnosing PCSM-LPD and a specificity of 76.5%. The positive predictive value (PPV) is equal to 81.8%, and the negative predictive value (NPV) is equal to 100%. The estimated accuracy is around 89%, with an FPR of about 22%,

TABLE 1: Comparison of dermoscopic parameters between PCSM-LPD cases and control group.

Parameters	Group 1 frequencies	Group 2 frequencies	Chi-square value	<i>p</i> -value	Sensitivity	Specificity
Pigment	0	0	0.0	1.0	–	–
Pigment colour	0	0	0.0	1.0	–	–
Vessel types	18/18	17/18	3.27	0.195	–	–
Vessels type	Serpentine: 18	Clods: 2, Coiled: 1, Glomerular: 1, Linear: 4, Dotted: 5, Serpentine: 4	21.90	0.00055	1.0	0.76
Vessel distribution	Branched: 9, Clustered: 3, Radial: 3, Serpiginous: 3	Branched: 3, Clustered: 2, Radial: 8, Serpiginous: 4	5.59	0.133	–	–
Keratin Plugs	16/18	14/18	23.20	< 0.001	0.889	0.778
Background colour	Yellow-orange: 18	Orange: 1, Red: 13, Yellow-orange: 4	22.91	< 0.001	1.0	0.778
Desquamation	4/18	7/18	0.52	0.469	–	–
Desquamation position	Diffuse: 2	Central: 1, Diffuse: 4, peripheral: 1	0.89	0.641	–	–

Note: This table presents the frequencies, chi-square values, *p* values, sensitivity, and specificity for various dermoscopic parameters observed in group 1 (PCSM-LPD cases) and group 2 (control group). Statistically significant differences were found in the types of vessels, presence of keratin plugs, and background colour.

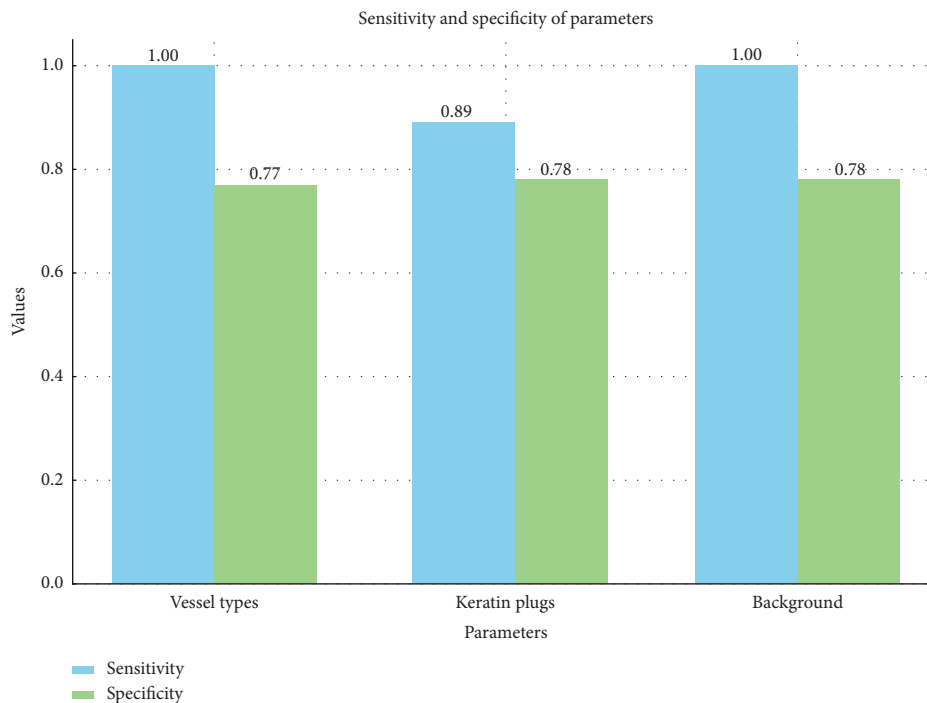


FIGURE 2: Graphical representation of dermoscopic features in PCSM-LPD and control group. This image illustrates the distribution and frequency of crucial dermoscopic characteristics, such as vessel types and background colours, highlighting significant differences between PCSM-LPD cases and other cutaneous lymphomas.

TABLE 2: Interoperator reliability analysis of dermoscopic variables.

Parameters	K operators 1–2	K operators 1–3	K operators 2–3
Vessels (yes/no)	0.915	0.915	0.824
Vessels type	0.144	0.098	0.350
Vessels distribution	0.203	0.038	0.168
Keratin plugs	0.678	0.522	0.363
Plugs type	0.276	0.203	0.243
Dots colour	0.060	0.654	0.031
Background colour	0.505	0.441	0.403
Desquamation	0.548	0.625	0.346
Desquamation localisation	0.382	0.396	0.347
Diagnosis	0.026	0.291	0.204

Cohen's Kappa	Interpretation
0	No agreement
0.10–0.20	Slight agreement
0.21–0.40	Fair agreement
0.41–0.60	Moderate agreement
0.61–0.80	Substantial agreement
0.81–0.99	Near perfect agreement
1	Perfect agreement

Note: This table displays Cohen's Kappa values indicating the level of agreement among three operators for different dermoscopic features. High agreement was observed for recognition of vessel presence and keratin plugs, while moderate to low agreement was seen for vessel type, distribution, and background colour.

an FNR = 0, an LR+ equal to 4.55, and an LR of 0. The diagnostic odds ratio (DOR) could not be calculated.

The identification of “Keratin plugs” is associated with a (sensitivity of 88.9%) and a specificity of 77.8%; consequently, it has an estimated PPV of 80%, an NPV of 87.5%, an accuracy of about 83%, about 22% of FPR, an FNR of 11%, LR+ equal to 4.95, and an LR of 0.141, the final DOR value is 28.

Lastly, the “yellow-orange” background has the following DAM in the detection of PCSM-LPD: sensitivity = 100%, specificity = 77.8%, PPV 81.8%, NPV = 100%, accuracy = 89%, FPR = 22%, FNR = 0, LR+ = 4.5, LR- = 0.

For some variables the DOR could not be expressed due to sensitivity or specificity reaching 100%, leading mathematically to an infinite ratio.

**3.2.2. Inter-Rater Reliability Analysis Using Cohen's Kappa.** The inter-rater reliability analysis using Cohen's Kappa is summarised in (Table 2) [17–19].

In regards to all dermoscopic variables related to pigmentation, the interobserver agreement was complete; identifying any vessel was associated with a high level of agreement between operators, with the lowest Kappa value being 0.824.

When defining the specific vessel types, operators showed a low-to-moderate level of agreement, with the lowest being 0.098 and the highest being 0.350. Similarly, we observed low agreement levels on the description of vessels' distributions (Kappa values were 0.203, 0.038 and 0.168 between operators 1 and 2, 2 and 3 and 1 and 3, respectively).

Identifying any keratin plug was associated with high agreement between operators, with Kappa values of 0.678, 0.522 and 0.363. In contrast, the description of the keratin plug's characteristics had moderate agreement across all pairs of operators, with Kappa values ranging from 0.203 to 0.276.

Lastly, the description of the background colour showed moderate agreement among all pairs of operators (with Kappa values ranging from 0.403 to 0.505). The attempt to make a precise diagnosis based on the dermoscopic image revealed low agreement among all pairs of operators, with Kappa values ranging from 0.026 to 0.291 (Figure 3).

## 4. Discussion

This study provides a comprehensive and structured analysis of dermoscopic patterns of PCSM-LPD, updating and improving our preliminary work published [8].

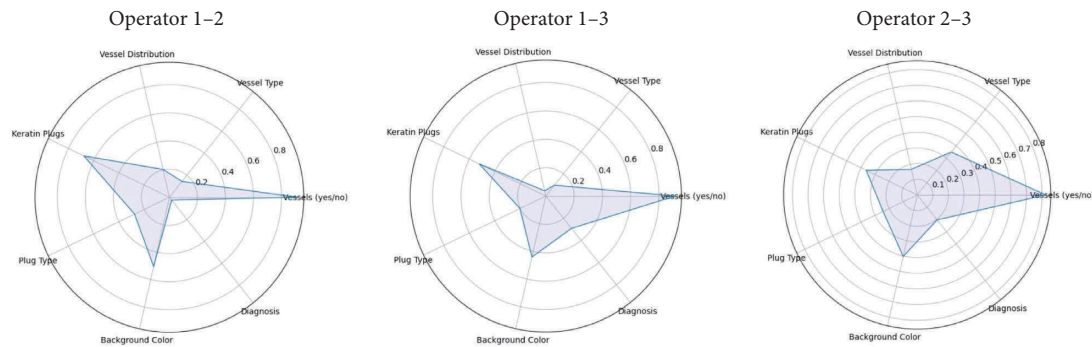


FIGURE 3: Radar charts show the interoperator reliability for dermoscopic features in PCSM-LPD. Each chart represents Cohen's Kappa values between pairs of operators. These charts emphasise the need for standardised training to improve diagnostic consistency.

The most informative variables that help distinguish PCSM-LPD from its clinical differential diagnoses are the presence of serpentine vessels, keratin plugs, and a yellow-orange background. PCSM-LPD exhibited a consistently observed of serpentine vessels, which was infrequently observed in the control group.

Keratin plugs were also significantly more prevalent in the PCSM-LPD group, appearing in 89% of cases compared to only 22% in the control group. This striking difference highlights the potential of keratin plugs as a dermoscopic clue. The sensitivity (89%) and specificity (78%) values suggest that while keratin plugs are a reliable clue for diagnosing PCSM-LPD, their absence does not definitively exclude this diagnosis.

The background colour also differed significantly between the groups. The PCSM-LPD group consistently showed a yellow-orange background, whereas the control group had a mix of orange, red, and yellow-orange backgrounds.

In keeping with all the available data from the literature, PCSM-LPD and all conditions that can go into differential diagnosis lack any pigmented structure on dermoscopy except for a few case reports [20].

The data from the literature on the use of dermoscopy in cutaneous lymphoproliferative disorders are scarce and primarily focused on more common conditions like MF and B cell lymphomas [21–25]; it is, therefore, challenging to make comparisons between our data and the previous works.

Our PCSM-LPD results corroborate the findings of Kittler et al. [13], who identified similar colour patterns in dermoscopic evaluations of PCSM-LPD [12].

The authors observed irregular linear vessels with peripheral distribution and centripetal orientation, which aligns with our findings regarding the significance of vascular patterns. They also described the ubiquitous presence of a salmon-pink homogeneous background, which supports the importance of background colour in the dermoscopic presentation of PCSM-LPD. However, their description differs from our observation, as, in our experience, these lesions tend to have a yellow-orange colour, which is histologically explained by the presence of a dense dermal infiltrate partially sparing the epidermis. Their study did not mention keratin plugs, which may depend on the lesions' morphology or anatomical site.

Even if our study findings partially align with the current literature and could reinforce the diagnostic value of specific dermoscopic features, we suggest caution: inter-rater reliability analysis revealed high variability in interobserver agreement among operators for most of the considered dermoscopic features, even when using standardised terminology and a high degree of training. Specifically, the low Kappa values observed for vessel type, vessel distribution, and keratin plug characteristics emphasise the intrinsic complexity of dermoscopic assessment in rare cutaneous diseases such as CTCLs. Due to the intrinsic rarity of these conditions, clinicians are not routinely exposed to such cases and therefore lack consistent familiarity with applying dermoscopy to their evaluation, which inevitably limits interobserver agreement. This variability emerged despite the use of standardised IDS terminology and the involvement of experienced dermatologists, highlighting how operator-dependent interpretation remains a significant limitation and indicating that, beyond the intrinsic subjectivity of dermoscopic evaluations, there are practical challenges concerning the feasibility of consistently applying some criteria in routine practice.

This highlights the need for standardised training and protocols in dermoscopic evaluation to ensure consistent and reliable diagnoses across different operators. In this regard, the work of Kittler et al. [13] on dermoscopic terminology and standardisation provides a reference framework that supports our methodological approach, validates our findings [15] and underlines the importance of standardised terminology in achieving reliable diagnostic outcomes, which, despite this, are often challenging to obtain [13, 25]. We recognise that the lower frequency of serpentine vessels and yellow-orange background in our control group may contrast with previous findings. This discrepancy is likely related to the blinded evaluation setting and to our inclusion criteria [26, 27], which encompassed a range of different cutaneous lymphoproliferative disorders and was considered given the rarity of PCSM-LPD and the small, balanced sample size used for case-control comparison.

Our study has strengths and limitations: One of the primary strengths is the systematic and double-blind evaluation of dermoscopic images by multiple experienced dermatologists, which enhances our findings' reliability and validity. Using

a control group comprising various cutaneous lymphomas that clinically resemble PCSM-LPD allowed us to highlight the dermoscopic criteria that differentiate PCSM-LPD from the others; the use of a 1:1 ratio, while methodologically justified, may represent a limitation by reducing the potential robustness achievable with a larger and more diverse control group. Additionally, DAMs provide quantitative support to address the diagnostic utility of such features.

Study limitations accounted for a relatively small sample size and the retrospective design, which may have limited the generalisability of our findings. However, being considered a rare affection, the case-control study remained the most suitable study design for this analysis. More studies with more diverse populations are necessary to broaden the dermoscopic variables and improve the current DAMs. Still, we cannot underline how the study's retrospective nature may introduce selection bias, even if a standardised nomenclature has been used for the evaluation, as only cases referred to our unit were included. Furthermore, the absence of systematic matching of lesions by anatomical site or morphology and the heterogeneity of the control group represent additional trade-offs. A 1:1 case-to-control ratio was adopted to preserve statistical symmetry and avoid overweighting the controls, but this may have reduced the robustness of the comparisons. These limitations reflect the rarity of PCSM-LPD and the constraints of retrospective data collection, and they underline the need for larger, prospectively matched cohorts to confirm these preliminary findings.

## 5. Conclusion

This work aimed to evaluate the dermoscopic features of PCSM-LPD comprehensively and to identify dermoscopic features that may help differentiate PCSM-LPD from other clinically similar conditions.

The dermoscopic features identified, serpentine vessels, keratin plugs, and a yellow-orange background, seemed promising clinical clues to help with the challenging diagnosis of PCSM-LPD yet require further studies to confirm their actual usability.

However, even if our data highlights the potential value of these novel criteria, we also encountered a very low interoperator concordance. Further analyses on larger, dedicated prospective studies are needed to ensure their practical use in a real-life setting.

## Data Availability Statement

Data are available on request from the authors.

## Ethics Statement

This study was approved by the no Clin.Isto. Tp.19, Bologna local ethical committee.

## Consent

The patients in this manuscript have given written informed consent to the publication of their case details.

## Conflicts of Interest

The authors declare no conflicts of interest.

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The authors have nothing to report.

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