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ORIGINAL ARTICLE

Clinical and dermatoscopic predictors of squamous cell carcinoma of the lips: a case-control, multicentric study

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Abstract

Background Squamous cell carcinoma of the lip accounts for 20% of all oral carcinomas. Its diagnosis may be challenging because it clinically resembles actinic cheilitis and inflammatory lesions of the lips.

Objectives To determine clinical and dermatoscopic predictors of squamous cell carcinoma of the lip vs. other lip lesions.

Methods Multicentre retrospective morphological study, including histologically confirmed cases of squamous cell carcinoma of the lip and controls consisting of actinic cheilitis and inflammatory lesions of the lips. Clinical and dermatoscopic images were evaluated for the presence of predefined criteria. Crude and adjusted odds ratios and corresponding 95% confidence intervals were calculated by univariate and multivariate logistic regression respectively.

Results A total of 177 lip lesions were evaluated, 107 (60.5%) were squamous cell carcinomas and 70 (39.5%) were controls. The most frequent dermatoscopic criteria of lip squamous cell carcinoma were scales (100%), white halos (87.3%) and ulceration (79.4%). The majority of squamous cell carcinomas displayed polymorphic vessels (60.8%), with linear (68.6%) and hairpin (67.6%) being the most frequent types. Multivariate logistic regression analysis showed that clinical predictors of lip squamous cell carcinoma were exophytic appearance and clinical hyperkeratosis, with 43-fold and 6-fold higher probability respectively. White clods and ulceration in dermoscopy presented a 6-fold and 4-fold increased risk for squamous cell carcinoma respectively.

Conclusions A scaly lesion with exophytic growth, dermatoscopically displaying white clods, ulceration and linear and hairpin vessels is very likely a squamous cell carcinoma of the lip.

Keywords: actinic cheilitis, cheilitis, dermatoscopy, differential diagnosis, lips, squamous cell carcinoma.
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Conflicts of interest

The authors have no conflict of interest to declare.

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Introduction

Squamous cell carcinoma (SCC) accounts for 90% of oral malignancies and 2 of 10 oral SCCs are located on the lips. Lips SCC (LSCC) is more common in men, has a predilection for the lower lip and a peak of occurrence between the sixth and seventh decade.[1,2] The probability of loco-regional and distant metastasis of LSCC (3%–20%) is higher compared to cutaneous SCC (CSCC).[3]

Chronic sun exposure is considered the most potent risk factor, meaning that outdoor and rural workers are the professions at higher risk. The usual precursor of LSCC is actinic cheilitis (AC). AC represents an in-situ dysplasia and it is considered premalignant due to the risk of progression into invasive LSCC.[2]

The discrimination between AC and invasive carcinomas solely on a clinical basis is considerably challenging.[3] Although dermatoscopy has become an essential tool for the evaluation of skin tumours and the dermatoscopic criteria for CSCC have been well described,[4,5] little is currently known about the dermatoscopic features of LSCC.[6,7]

The aim of our study was to investigate the clinical and dermatoscopic criteria of LSCC and to identify potent clinical and dermatoscopic predictors for its differentiation for AC and other types of cheilitis.

Methods

This retrospective morphological study was conducted in four Dermato-oncology units in Europe. Ethics committee approval was waived, as the study did not affect the routine diagnostic or therapeutic procedure.

We retrospectively reviewed records of patients with LSCC, AC and other inflammatory or neoplastic diseases involving the lip vermillion, diagnosed from 01/01/2018 to 31/12/2019. Inclusion criteria were as follows: (i) a definite histologic diagnosis, (ii) availability of high-resolution clinical and dermatoscopic images at baseline. Cases with an ambiguous histological diagnosis and individuals that had received previous treatment were excluded.

Dermatoscopic images were captured using a digital camera with an attached dermatoscopic lens (DermLite Photosystem, 3Gen) at 10-fold magnification. Minimal pressure was applied and an immersion gel was used to avoid alterations concerning the morphology of capillaries and ensure their visualization.

The clinical and dermatoscopic images were randomized and evaluated by two independent and blinded of histopathologic diagnosis investigators for the presence of predefined criteria. A third investigator was involved in case of disagreement. The clinical and dermatoscopic variables were selected based on previously published evidence.[6–10]

Statistical analysis

For the purpose of the analysis, all LSCC cases served as cases and all the remaining lesions as controls. All separate clinical and dermatoscopic variables were included in the analysis. Categorical data are presented as numbers and frequencies and were compared using Pearson's Chi-squared test. Relative risks for all dichotomous variables were approximated by odds ratios (OR). Crude and adjusted OR and corresponding 95% confidence intervals (95% CI) were calculated by univariate and unconditional multivariate logistic regression respectively. Alpha level was set at 0.05 and an alpha level of 0.20 was used as cut-off for variable removal in the automated model selection for multivariate logistic regression. 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, Armonk, NY, USA: IBM Corp).

Results

We retrospectively reviewed patients records and detected 223 patients who underwent a biopsy for a dermatologic disease involving the lip vermilion. Among them, a total of 177 met inclusion criteria. Forty-six patients were excluded due to lack of clinical and/or dermatoscopic images. The study population consisted of 76.8% men and 23.2% women. The mean age at diagnosis was 72.2 years (SD: 16.2; range: 26–28 years). In the group of LSCC, the mean age was higher (76.6 $\pm$ 10.5). One hundred and seven of 177 (60.5%) lesions corresponded to LSCC and 70 (39.5%) to non-LSCC. In the group of non-LSCC, there were 51 cases of AC (72.8%), 10 (14.3%) of exfoliative/eczematous cheilitis (EC), 3 (4.3%) of lichen planus (LP), 2 (2.9%) of lip involvement in patients with acute systemic lupus erythematosus (SLE) and 4 (5.7%) of chronic discoid lupus (CDLE). The most frequent anatomic site of involvement was the lower lip in LSCC (103/107; 96.3%), whilst in the control group, the corresponding rate was lower (62/70; 88.6%). Table 1 includes the epidemiological data and the clinical and dermatoscopic characteristics of the study population. Five patients from the LSCC group and nine patients from the AC group were excluded because of low quality of dermatoscopic images. As a result, in the dermatoscopic analysis, we included 102 of 107 LSCC (94.4%) and 42 of 51 AC (82.4%), as well as all the other cases.

As evidenced in Table 1, scales were found in 100% of the studied population, including groups, LSCC and controls. White halos were the second most frequent dermatoscopic feature, present in 87.3% and in 85.2% of LSCC and control group respectively. Ulceration was found in 79.4% of the LSCC and in 42.6% of controls, whilst erosions were seen in 51% and 80.3% of LSCC and controls respectively. Figures 1 and 2 illustrate the clinical and dermatoscopic aspects of two representative cases of LSCC and AC, correspondingly.

Most lesions in both groups displayed polymorphous vessels (60.8% of LSCC and 75.4% of control group). The most frequent morphologic types of vessels were linear (68.6% in LSCC and 55.7% in controls) and hairpin (67.6% in LSCC and 60.7% in controls).

Table 1 Epidemiologic characteristics and frequencies of clinical and dermatoscopic criteria in squamous cell carcinoma of the lips and controls

	LSCC *n* = 107	AC *n* = 51	EC *n* = 10	LP *n* = 3	CDLE *n* = 4	SLE *n* = 2	Total controls *n* = 70
Sex							
Females	16 (15%)	15 (29.4%)	6 (60%)	1 (33.3%)	3 (75%)	0	25 (37.7%)
Males	91 (85%)	36 (70.6%)	4 (40%)	2 (66.7%)	1 (25%)	2 (100%)	45 (64.3%)
Mean age	76.6 ± 10.5	69.9 ± 12.5	68.7 ± 21.3	36 ± 1.4	38 ± 8.2	38.5 ± 3.5	
Clinical variables							
Anatomic distribution							
Upper lip	3 (2.8%)	0	0	0	0	0	0
Lower lip	103 (96.3)	47 (92.2%)	8 (80%)	1 (33.3%)	4 (100%)	2 (50%)	62 (88.6%)
Both	1 (0.9)	4 (7.8)	2 (20%)	2 (66.7%)	0	0	8 (11.4%)
Number of lesions							
Solitary	59 (55.1%)	13 (25.5%)	3 (30%)	0	2 (50%)	0	18 (25.7%)
Multiple/multifocality	48 (44.9%)	38 (74.5%)	7 (70%)	3 (100%)	2 (50%)	2 (100%)	52 (74.3%)
Clinical morphology							
Flat	63 (58.9%)	49 (96.1%)	10 (100%)	3 (100%)	4 (100%)	2 (100%)	68 (97.1%)
Exophytic	44 (41.1%)	2 (3.9%)	0	0	0	0	2 (2.9%)
Clinical scale	62 (57.9%)	32 (62.7%)	7 (70%)	1 (33.3%)	1 (25%)	1 (50%)	42 (60%)
Clinical ulceration	77 (72%)	33 (64.7%)	8 (80%)	1 (33.3%)	3 (75%)	1 (50%)	46 (65.7%)
Clinical hyperkeratosis	34 (31.8%)	2 (3.9%)	0	0	1 (25%)	0	3 (4.3%)
Vermilion							
Normal	60 (56.1%)	42 (82.4%)	8 (80%)	2 (66.7%)	3 (75%)	2 (100%)	57 (81.4%)
Distorted	47 (43.9%)	9 (17.6%)	2 (20%)	1 (33.3%)	1 (25%)	0	13 (18.6%)
Dermatoscopic variables	***n* = 102**	***n* = 42**	***n* = 10**	***n* = 3**	***n* = 4**	***n* = 2**	***n* = 61**
Ulceration	81 (79.4%)	15 (35.7%)	7 (70%)	1 (33.3%)	2 (50%)	1 (50%)	26 (42.6%)
Erosion	52 (51%)	35 (83.3%)	8 (80%)	2 (66.7%)	2 (50%)	2 (100%)	49 (80.3%)
Scale							
Yellow	37 (36.3%)	13 (31%)	3 (30%)	0	3 (75%)	1 (50%)	20 (32.8%)
White	50 (49%)	23 (54.8%)	6 (60%)	2 (66.7%)	1 (25%)	0	32 (52.5%)
Both	15 (14.7%)	6 (14.3%)	1 (10%)	1 (33.3%)	0	1 (50%)	9 (14.8)
White structureless areas	53 (52%)	21 (50%)	2 (20%)	1 (33.3%)	2 (50%)	1 (50%)	27 (44.3%)
White streaks	10 (9.8%)	2 (4.8%)	1 (10%)	0	0	0	3 (4.9%)
White halos	89 (87.3%)	35 (83.3%)	9 (90%)	3 (100%)	3 (75%)	2 (100%)	52 (85.2%)
White clods	44 (41.1%)	2 (4.8%)	0	0	1 (25%)	0	3 (4.9%)
Vessels' pattern							
Monomorphous	40 (39.2%)	12 (28.6%)	2 (20%)	0	1 (25%)	0	15 (24.6%)
Polymorphous	62 (60.8%)	30 (71.4%)	8 (80%)	3 (100%)	3 (75%)	2 (100%)	46 (75.4%)
Vessels' type							
Dotted	27 (26.5%)	19 (45.2%)	6 (60%)	2 (66.7%)	3 (75%)	0	32 (52.5%)
Linear	70 (68.6%)	25 (59.5%)	5 (50%)	2 (66.7%)	2 (50%)	0	34 (55.7%)
Glomerular	4 (3.9%)	5 (11.9%)	2 (20%)	0	0	1 (50%)	8 (13.1%)
Hairpin	69 (67.6%)	23 (54.7%)	6 (60%)	3 (100%)	3 (75%)	2 (100%)	37 (60.7%)
Arborizing	3 (2.9%)	0	0	0	0	0	0
Comma	3 (2.9%)	2 (4.8%)	0	0	1 (25%)	0	3 (4.9%)

AC, actinic cheilitis; CDLE, chronic discoid lupus; EC, exfoliative/eczematous cheilitis; LP, lichen planus; LSCC, Squamous cell carcinoma of the lip; SLE, systemic lupus erythematosus.

The univariate logistic regression analysis revealed several clinical predictors of LSCC, including solitary lesion, exophytic appearance, clinical hyperkeratosis and distorted vermilion. Moreover, several dermatoscopic predictors, including ulceration, erosion and white clods, were detected.

Multivariate logistic regression was used to model the influence of clinical and dermatoscopic criteria on LSCC diagnosis, the main positive clinical predictors were exophytic appearance and clinical hyperkeratosis exhibiting 43-fold and a 6-fold probability respectively (Table 2). Among the dermatoscopic

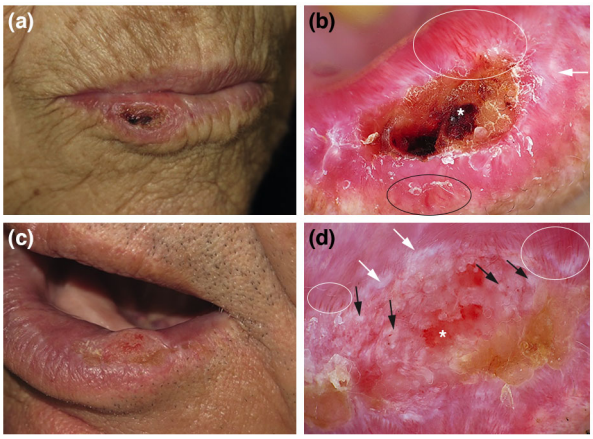

Figure 1 The clinical aspect of a lip squamous cell carcinoma (a), dermatoscopically characterized by the presence ulceration (white star), linear (black circle) and hairpin (white circle) vessels and white structureless areas (white arrow) (b). A lip squamous cell carcinoma (c), dermatoscopically displaying ulceration (white star), hairpin vessels (white circles), as well as white clods (black arrows) (d).

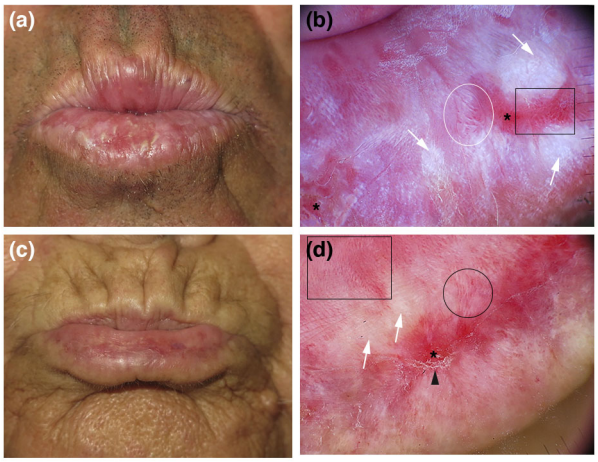

Figure 2 Clinical aspect of two lesions of actinic cheilitis (a, c), dermatoscopically (b, d) displaying erosions (black star), dotted (black square) and hairpin vessels (white circle), as well as white structureless areas (white arrows) and white scales (black arrowhead).

predictors, white clods and ulceration presented a 6-fold and 4-fold increased risk for LSCC respectively (Table 2). Applying a filter to compare only clinically flat SCCs to controls, dermatoscopic ulceration retained its diagnostic significance ($P = 0.044$, OR = 6.2) and white clods showed a trend ($P = 0.111$, OR = 2.3) towards predicting LSCC.

Table 2 Adjusted clinical and dermatoscopic predictors for squamous cell carcinoma of the lips

Variable	95% C.I. for OR			
Clinical characteristics	***P*-value**	**OR**	**Lower**	**Upper**
Age	0.017	1.056	1.010	1.104
Lower lip	0.030	0.075	0.007	0.774
Exophytic appearance	0.001	49.679	4.705	524.603
Hyperkeratosis	0.025	8.605	1.311	56.470
Dermatoscopic features	***P*-value**	**OR**	**Lower**	**Upper**
Ulceration	0.007	4.115	1.466	11.553
White clods	0.042	6.376	2.344	12.503

OR: Odds Ratio approximated via multivariate logistic regression. *P*-values and confidence intervals (CI) adjusted for the remainder of variables included in the model. Statistical significance typed in bold.

Discussion

Opposed to AC and inflammatory cheilitis that are mainly managed by non-surgical approaches, LSCC requires surgical excision, workup for staging and close monitoring of the patient. In this context, differentiation of LSCC from other diseases affecting the lips is extremely important. In the current study, we were able to identify clinical and dermatoscopic predictors of LSCC that may prove useful in discrimination of LSCC from other entities, including AC.

The mean age at diagnosis was significantly higher for LSCC, which is in line with the literature.[11–14] The most frequent location for both LSCC and non-LSCC lesions was the lower lip, with a rate of 96.3% and 88.6% respectively.

Concerning clinical morphology, an exophytic growth was observed in 41.1% of LSCC, whilst the vast majority (97.1%) of non-LSCC appeared as flat lesions. Multivariate analysis confirmed that an exophytic appearance represents a potent LSCC predictor, posing a 41-fold increased risk. This finding is reasonable, considering that invasion of the dermis by the neoplastic cells results in elevation of the skin surface, reflecting a vertical growth phase of the tumour.

Interestingly, clinical hyperkeratosis was also a strong predictor of LSCC, being present in 31.8% of LSCCs and in only 4.3% of the controls. The latter is in line with previous studies suggesting that the clinical and dermatoscopic presence of keratin is a strong predictor of invasive cSCC, and particularly of well-differentiated cSCC.[4,5,10] In our study, we did not perform subanalysis according to the degree of histological differentiation, thus we are not able to comment on possible correlation of hyperkeratosis and grade of differentiation.

In terms of dermatoscopy, the two most frequent criteria were scales and white halos. However, since these features were found at similar rates in both groups, they seem insufficient to assist the differential diagnosis. Similarly, dermatoscopic scales were found in all tumours of both groups, which is in agreement with previously published studies on LSCC.[6,7,15] It seems that desquamation, histopathologically corresponding to parakeratosis/

hyperkeratosis, may represent a non-specific reaction of the vermilion epithelium in several triggers, ranging from injuries to inflammatory and neoplastic diseases.[16]

White clods were significantly more frequent in LSCC and represented a significant predictor of its diagnosis. This is expected given that white clods represent foci of neoplastic keratinization within a well-differentiated tumour.

White circles are considered as a specific dermatoscopic clue for diagnosis of invasive cSCC and histopathologically correspond to acanthosis and hypergranulosis of the infundibular epidermis.[4] However, since the lips lack hair follicles, this important feature cannot be seen in LSCC, rendering its diagnosis more challenging.

Dermatoscopic ulceration was found in 74.4% of LSCCs and was associated with a 4-fold increased risk of LSCC. In contrast, dermatoscopic erosion was found in 83.3% of AC and 51% of LSCC. This finding is explained by the fact that AC is an in-situ neoplasm that may result in partial loss of the epidermis (erosion), whilst LSCC invades the dermis, resulting in full loss of the epidermis. The latter is in line with the proposed model of progression from actinic keratosis to invasive cSCC, in which ulceration is considered to reflect a phase of dermal invasion.[10] However, considering that discriminating an erosion from a superficial ulceration might be challenging, a biopsy remains mandatory in equivocal lesions.

In regards with the vascular pattern, linear and hairpin vessels were mostly seen in LSCC. Published data suggest that presence of irregular linear or hairpin vessels in cSCC may indicate a vertical growth phase of the tumour.[10] In our sample, polymorphous vessels were seen in high rates in both groups. The latter might be attributed to the specific anatomic characteristics of the lip vermilion, including the thin epithelium, that facilitate the visualization of the rich vascular network in the upper dermis.[17]

The discrimination between AC and LSCC is of paramount importance for the patient since the management and prognosis are different. Dermatoscopic features of AC have been only described in a few case reports.[8,9,18] The most common dermatoscopic structures described in AC include whitish structureless areas with scales and white halos of the vermilion of the lip.[8,9] An additional criterion found in the literature is radially arranged vascular telangiectasia surrounding the eroded areas.[18] In the group of AC in our sample, we dermatoscopically observed white halos in 83.3%, erosions in 83.3%, white scales in 54.8% and white structureless areas in 50% that are consistent with the existing literature. Furthermore, our study showed that only 17.6% of individuals with AC had vermilion distortion, whilst 82.4% maintained the normal vermilion architecture. The latter criteria could be useful in discrimination of AC vs. SSC.

A literature research revealed that there is a lack of studies reporting dermatoscopic features of inflammatory lesions involving the lip vermillion, such as EC, LP and CDLE.[19] Although it was not the main objective of our study, we found that the most frequent dermatoscopic findings in EC were ulceration, erosion, white scales, white halos and dotted and hairpin vessels. LP was characterized by hairpin vessels and white halos and CDLE by yellow scales, white halos and dotted and hairpin vessels (Table 1). An additional diagnostic clue derives from epidemiology, since opposed to LSSC and AC, these entities mostly affect younger population. Further studies, focusing on dermatoscopic criteria of inflammatory dermatoses occupying specific anatomic sites like the lip vermillion, are certainly needed in order to reach safe conclusions.

Our study has several limitations. The retrospective design induces a selection bias and the inclusion of histopathologically confirmed cases only induces a confirmation bias and might have resulted in a low representation of some frequent benign entities in our sample. Also, LSCC in our study was highly differentiated. In the light of these limitations, our results should be cautiously interpreted, especially in terms of the calculated specificity of each dermatoscopic feature.

In conclusion, our findings suggest that the clinical and dermatoscopic profile of a patient with a LSCC is an elderly man, with a scaly, exophytic lesion on the lower lip, dermatoscopically displaying ulceration, white clods and linear and hairpin vessels.

Acknowledgement

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

Data availability statement

All data related to this study are available upon request from the authors.

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