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(RESEARCH ARTICLE)

Clinical characteristics of oral mucosal lesions in patients with systemic lupus erythematosus and their association with clinical and laboratory parameters

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Abstract

Introduction. Systemic lupus erythematosus (SLE) is an autoimmune disease that includes a broad spectrum of mucocutaneous manifestations.

Objectives. To characterize the clinical spectrum of oral mucosal lesions in patients with SLE and to analize their association with clinical and laboratory parameters.

Methods. We performed a cross-sectional study with systematic oral evaluations in SLE adult patients. Systemic and cutaneous lupus activities were recorded. We collected epidemiologic, clinical, and laboratory data. Statistical analysis included the kappa coefficient, X2 test, Fisher's exact test and Mann-Whitney U-test, adjusting for multiple comparisons according to Bonferroni's method.

Results. A total of 181 patients (92.8% females) were included, with a median age of 37 (range 16-76) years. Cutaneous, systemic, and oral manifestations of lupus erythematosus (LE) activity were found in 31.5%, 23.8% and 18.8% of patients, respectively. Higher titres of anti-double-stranded (ds) DNA antibodies were detected in patients with LE-related oral lesions (LEOL) when compared to those without LEOL [356 (82-1083) UI vs 45 (0-417) UI; p=0.02). LEOL did not correlate to cutaneous (k=0.380) nor systemic (k=0.228) LE-activity (p<0.01).

Conclusions. Oral manifestations related to SLE were significantly associated to anti double-ds DNA antibodies. LEOL were independent of cutaneous and systemic activity.

Keywords: Mouth diseases; Lupus; Prevalence; Anti-dsDNA antibodies

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1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of various autoantibodies such as antinuclear and anti-ds DNA (anti-dsDNA) [1,2]. Lupus erythematosus (LE) includes a broad spectrum of manifestations, from a cutaneous-limited type (CLE) to a systemic type. SLE can affect virtually every organ. Lesions of the oral mucosa can be found in both SLE and CLE [3,4]. In LE, the mouth is usually affected both by the disease and by its treatment [5].

There are currently few studies addressing the oral mucosal lesions in patients with SLE, and the reported prevalence of LE-related oral lesions (LEOL) vary widely [3,5]. In previous reports, methodological aspects such as the involved specialists, study population, study objective, and operational definitions have resulted in an inconsistent frequency and in different descriptions of LEOL [6-9].

Thus, the objective of this study was to characterize the clinical spectrum of LEOL and its relation with certain clinical and laboratory parameters in SLE patients seen in a tertiary health care center.

2. Methods

A cross-sectional and analytic study was performed in our center from 2006-2014. Inclusion criteria to the study were subjects >18 years old with a confirmed diagnosis of SLE according to international criteria [10,11], who attended to the Dermatology Clinic and willingly signed an informed consent form. Exclusion criteria included cutaneous LE without SLE, HIV-infected patients, pharmacologic immunosuppression for any reason other than LE management, and inability to perform a complete mouth inspection. The study was approved by the research and ethics committee of our institution.

A systematic oral examination was performed by an oral pathologist. We used standardized clinical criteria for the diagnosis of mouth diseases. The aforementioned diagnoses were confirmed by cytology, histopathology, or laboratory, as applicable. We routinely took smears from oral lesions with clinical suspicion of candidal or herpetic origin; the samples were fixed in alcohol and stained with periodic acid Schiff or Papanicolaou, respectively [12,13]. The clinical diagnosis of LEOL was based on previously published descriptions [4,14] and differential diagnosis was emphasized. Pictures of the oral findings were taken.

We registered local irritating factors in the mouth such as use of dentures; presence of dental, orthodontic, or prosthetic cutting edges; daily use of mouthwash, smoking, and alcohol consumption. Heavy alcohol drinking was defined as daily alcohol ingestion or intoxication >once weekly. Oral hygiene status was determined according to the simplified oral hygiene index [15]; we considered an index <1.0 as good oral hygiene and >1.0 as poor oral hygiene.

We recorded the reason for dermatologic consultation, initial manifestation of LE, time elapsed from LE onset to diagnosis, number of physicians consulted prior to LE diagnosis, and history of LEOL. Cutaneous LE lesions were simultaneously evaluated by dermatologists, according to reported criteria [16-18].

From the medical chart, we obtained data of current LE systemic activity (<2 weeks prior to inclusion to the study) as reported by the treating rheumatologist [19,20]; current treatment for LE; use of any antibiotics or antimycotics in the 30 days prior to oral exam. Laboratory data included a hemogram (+ 15 days); anti-dsDNA antibodies, complement C3 and C4 (+ 3 months).

2.1. Statistical analysis

Medians and interquartile intervals for dimensional variables and percentages for categorical variables were used.

In order to facilitate registry and analysis, LEOL were grouped according to their predominant characteristic observed in clinical descriptions. The most frequent LEOL were classified into one of the following groups: erosions, ulcers, white reticular patches or plaques, erythematous plaques, and telangiectasias. We classified oral hyperpigmentations in three groups: as racial/physiologic, diffuse (including smokers' melanosis, post inflammatory hyperpigmentation and drug related hyperpigmentation) or melanocytic macules. All oral lesions were analysed by group and individually.

Most variables were dichotomized in order to simplify the statistical analysis. LE activity was evaluated according to its extent (oral, cutaneous or systemic activity), and according to the clinical presentation of the lesions. Subjects without LE activity were considered as controls (not-exposed).

Kappa test was used to appraise the concordance among LEOL and cutaneous or systemic activity. The non-parametric Mann-Whitney's U test was used for the comparison of laboratory values in patients with and without active LE; statistical significance was set at alpha 0.05, two-tailed.

We used X2 or Fisher's exact test to determine association between LE activity (oral, cutaneous, or systemic) and other variables, adjusting for multiple comparisons according to Bonferroni's method [21] to estimate the strength of the association in which the alpha value was established at 0.003.

3. Results

A total of 181 SLE patients were included; 168 (92.8%) females and 13 (7.2%) males, with a median age of 37 (range 16-76) years. The clinical and laboratory characteristics of the patients are described in table 1.

Table 1 Clinical and laboratory characteristics of 181 patients with lupus erythematosus.

	n	**(%)**	
Diagnosis of lupus:			
Systemic	159	(82.4)	
Systemic & discoid	22	(11.4)	
*Current treatment for lupus**	136	(76.8)	
Prednisone (n= 178)	91	(51.1)	
Antimalarial drugs (n=156)	70	(44.9)	
Azathioprine (n=174)	51	(29.3)	
Methotrexate (n=180)	7	(3.9)	
Local irritating factors			
Tobacco habit (n=177)	60	(33.9)	
Alcohol consumption (n=176)			
Occasional	46	(26.1)	
Strong	3	(1.7)	
Oral rinses use (n=173)	59	(34.1)	
Prosthetic tools (n= 145)			
Fixed	43	(29.7)	
Removable	18	(12.4)	
Both	8	(5.5)	
Cutting edges (n= 120)	49	(40.8)	
Oral hygiene (n=141)			
Good hygiene	91	(64.5)	
Poor hygiene	50	(35.5)	
Laboratory values:	*Median*	*Range*	
Leukocytes [K/mL] (n=165)	4.9	(2.7-13.8)	
Hemoglobin [g/dL] md (n=165)	13.4	(4.5-17)	
Platelets [K/mL] (n=163)	240	(17-491)	
Anti-dsDNA [UI] (n=68)	111	(0-2927)	
C3 [UI] (n=70)	75.8	(1.5-141)	
C4 [UI] (n=67)	11.3	(1.7-511)	

* Includes azathioprine, prednisone, hydroxichloroquine/chloroquine and/or methotrexate

A total of 51 (29.5%) patients (n=173) consulted for CLE manifestations; 19 (11.0%) consulted for CLE and other dermatoses, and 103 (59.5%) had a variety of other skin conditions. The initial manifestation of SLE (n=174) was cutaneous in 55 (31.6%) cases, arthritis in 51 (29.3%), oral lesions in 23 (13.2%), hematologic in 11 (6.3%), renal in

seven (4.0%), neurologic in seven (4.0%), and serositis in five (2.9%) patients. LE diagnosis (n=110) coincided with pregnancy in 20 (18.2%) patients. The median delay to LE diagnosis (n=158) was six (range 0-288) months and a median of three (range 1-30) physicians (n=104) were consulted before the diagnosis was established. According to the medical records, patients recalled a (n=177) previous history of LEOL in 111 (62.7%) cases.

Lupus-related manifestations are described in Table 2. Oral mucosal abnormalities were found in 174 (96.1%) patients; 34 (18.8%) of them coursed with LEOL. The most common presentations of LEOL are depicted in Figure 1A-G. Telangiectasias were the most frequently observed subtype of LEOL (n=14), they were characterized by multiple flat, millimetric, round, red lesions, sometimes spidery in appearance, distributed on the palate (n=9), lip mucosa (n=3), and/or buccal (n=2) mucosa (Figure 1A).

Table 2 Lupus erythematosus-related manifestations in 181 patients.

	n	**(%)**	
Skin	57	(31.5)	
Specific			
discoid lupus	21	(11.6)	
lupus profundus	5	(2.8)	
subacute lupus	3	(1.7)	
chilblain	1	(0.5)	
bullous	1	(0.5)	
Non-specific			
photosensitivity	16	(8.8)	
vasculitis	15	(8.3)	
diffuse alopecia	3	(1.7)	
pustular lesions	1	(0.5)	
not specified	9	(5.0)	
Systemic	43	(23.8)	
articular	22	(12.1)	
hematologic	10	(5.5)	
renal	8	(4.4)	
other*	6	(3.3)	
not specified	3	(1.7)	
Mouth	34	(18.8)	
telangiectasia	14	(7.7)	
erosion	11	(6.1)	
ulcer	6	(3.3)	
white reticular patch	7	(3.9)	
erythematous plaque	7	(3.9)	
other**	5	(2.8)	

* Includes neurologic (3 patients), immunologic (2 patients), serositis (1 patient)
** Includes erythema (2 patients), atrophy (2 patients) and edema (1 patient)

Erosive lesions were observed in eleven patients, and were located on hard palate (n=5), gingiva (n=4), and buccal mucosa (n=4), vermilion border (n=3), lip mucosa (n=2), and retromolar (n=1) area (Figure 1B). Oral ulcers were seen in six subjects, and were superficial, well-delimited, clean-based, with angled irregular borders, surrounded or not by erythema or erosive slightly keratinized margins; they affected mainly the central area of hard palate (n=4), labial mucosa (n=4), distal area of the buccal mucosa (n=2), and vermilion (n=1) border; (Figure 1C).

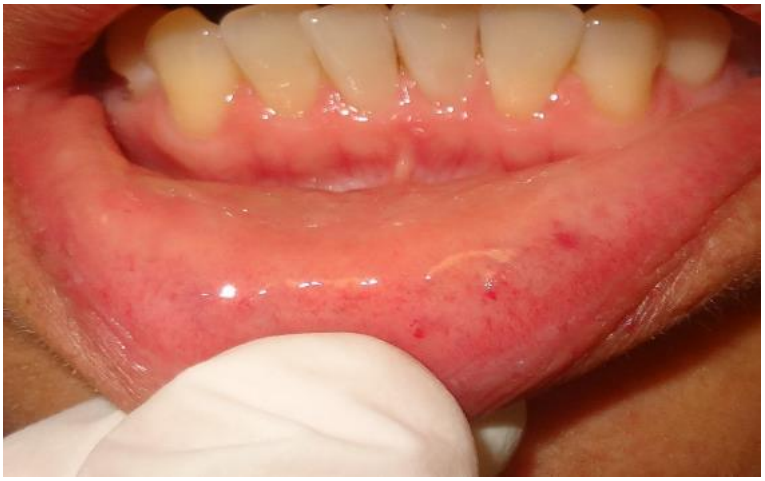

Figure 1A Multiple telangiectasias on labial mucosal surface and vermillion border of the lower lip.

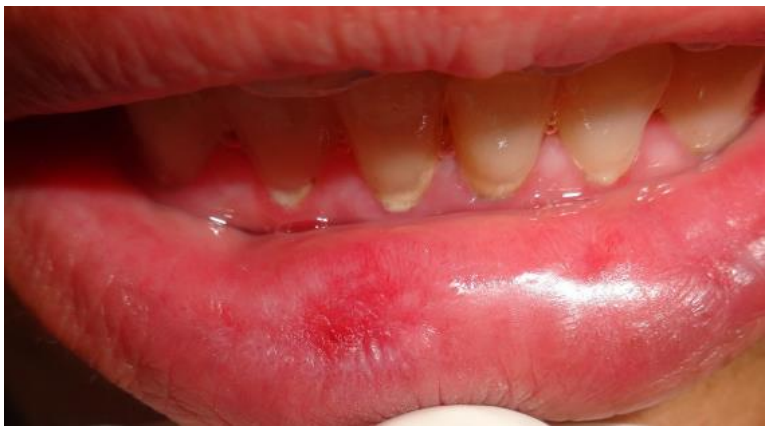

Figure 1B Erosions affecting lower labial mucosa and vermillion border of the lower lip, surrounded by a white reticular margin.

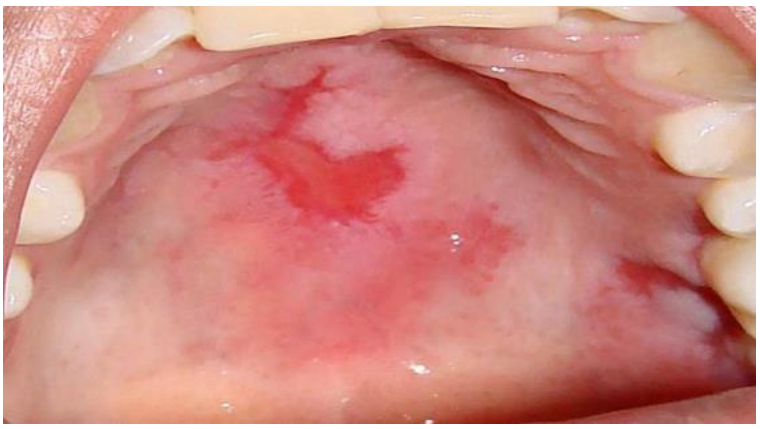

Figure 1C Typical ulceration in lupus erythematosus, with irregular erythematous margins and fine scales, involving the central hard palate area.

White reticulate patches were seen in seven patients, and were located on buccal mucosa (n=4), ventral tongue (n=3), and lip mucosa (n=2); these lesions were mainly bilateral, with marked or discrete millimetric white lines in the buccal area (Figure 1D), but with an apparent fibrous pattern when these were located on the ventral surface of the tongue (Figure 1E).

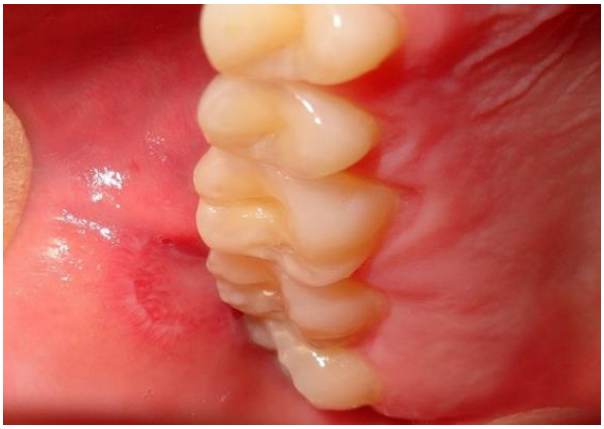

Figure 1D White reticular plaque located in right buccal mucosa.

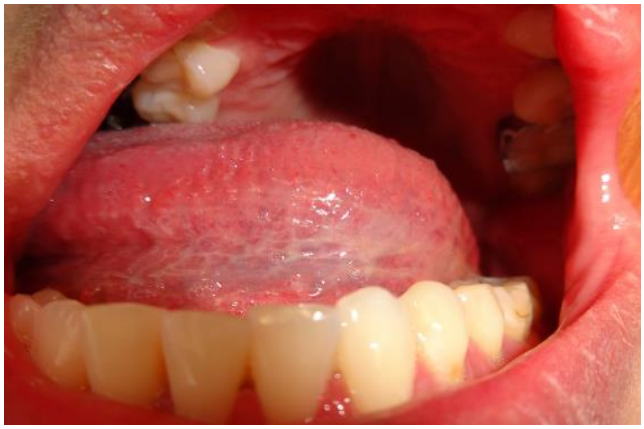

Figure 1E Reticular plaque with a cicatricial aspect, affecting left ventral surface of the tongue.

Erythematous plaques (n=7) were red inflamed patches (Figure 1F); some of them with scaling, crusty appearance (Figure 1G), and exclusively involving the vermilion borders of the lip. Other oral mucosal manifestations of lupus included erythema on the hard palate and retromolar buccal mucosa (n=2); vermilion atrophy (n=2) and lip edema (n=1). The frequency of all oral findings is detailed in Table 3.

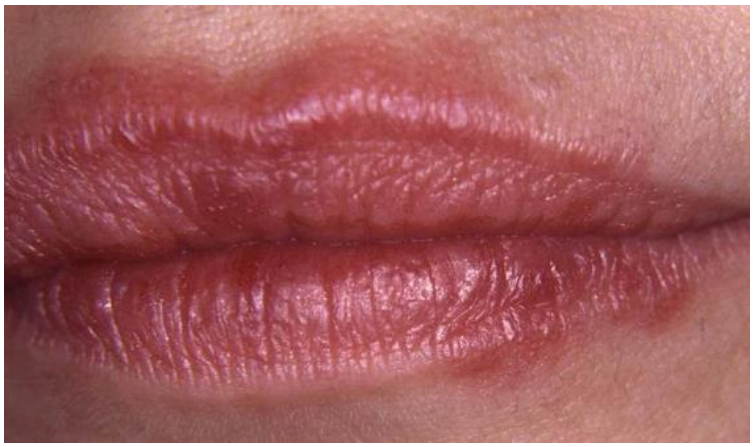

Figure 1F Erythematous plaques distributed on vermillion borders and skin of lips**.**

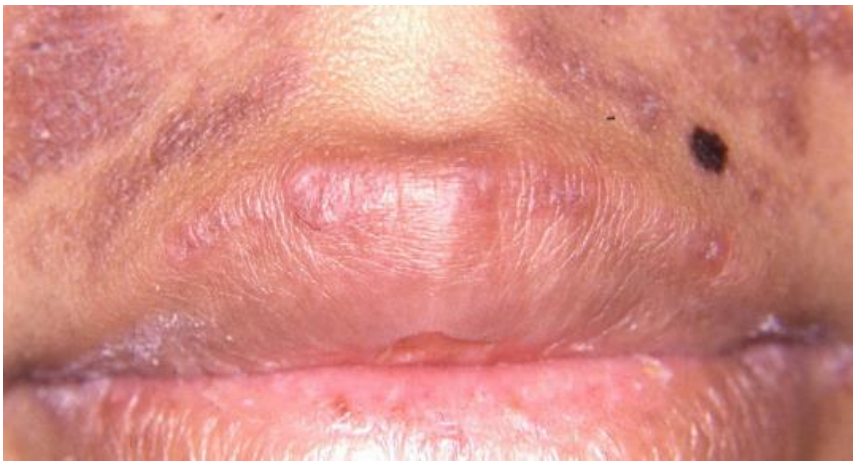

Figure 1G Red-rose plaques with fine scale, located on upper vermillion border of the lip.

Table 3 Frequency of oral mucosal conditions in 181 patients (pts) with lupus erythematosus.

Oral lesion		n	(%)
Lupus erythematosus-related lesions		34	(18.8)
Infections by causal agent			
	Candidosis[1]	50	(27.6)
	HPV[2]	3	(1.7)
	Fistula[3]	3	(1.7)
	Hairy leukoplakia	2	(1.1)
	Herpes simplex virus	1	(0.5)
	Herpes zoster virus	1	(0.5)
Miscelaneous			
	Hyperpigmentation	100	(55.2)
	racial/physiologic	62	(34.2)
	diffuse (drug related)	19	(10.5)
	melanocytic macules	19	(10.5)
	Coated tongue	44	(24.3)
	Paleness	40	(22.1)
	Xerostomia	39	(21.5)
	Fissured tongue	26	(14.4)
	Exfoliative cheilitis	23	(12.7)
	Traumatic erosion	21	(11.6)
	Erythema *migrans*[4]	16	(8.8)
	Frictional keratosis	13	(7.2)
	Scar	13	(7.2)
	Fibrous hyperplasia	8	(4.4)
	Fordyce's spots	8	(4.4)
	Varix	7	(3.9)
	Leukoedema	7	(3.9)
	Traumatic ulcer	7	(3.9)
	White occlusal line (*linea alba*)	6	(3.3)
	Mucosal exfoliation (chemical burns)	6	(3.3)
	Mucous retention phenomenon[5]	5	(2.8)
	Tongue indentation	4	(2.2)
	Morsicatio buccarum/labiorum	4	(2.2)
	Tongue atrophy[6]	3	(1.7)
	Hairy tongue	3	(1.7)
	Recurrent aphthous ulcers[7]	2	(1.1)
	Intramucous nevus	1	(0.5)
	Idiopatic leukoplakia	1	(0.5)
	Smoker's palate	1	(0.5)
	Amalgam tattoo	1	(0.5)

1 Includes erythematous (38 pts), denture-related (9 pts), angular cheilitis (6 pts), pseudomembranous (4 pts), related to inflammatory papillary hyperplasia (2 pts) and chronic hyperplastic (1 patient) candidosis.
2 Includes Heck's disease (2 pts) & squamous cell papilloma (1 patient); **3** Dental and periodontal origin.
4 Includes tongue (15 pts), buccal and tongue (1 patient); **5** Includes mucocele (3 pts), ranula (1 pt) & maxillary sinus cyst (1 patient).
6 Nutritional deficiency related. **7** Includes minor & major (1 patient), minor (1 patient) presentation.

Table 4 Laboratory values in patients with and without lupus erythematosus activity.

Laboratory values	Lupus erythematosus activity																			
	Mouth							Skin							Other*					
	Activity			No activity				Activity			No activity				Activity			No activity		
	n	Md	(Q1-Q3)	n	Md	(Q1-Q3)	p	n	Md	(Q1-Q3)	n	Md	(Q1-Q3)	P	n	Md	(Q1-Q3)	n	Md	(Q1-Q3)	p
Leukocytes (K/mL)	36	4.4	(3.7-4.9)	136	5.1	(4.3-7.0)	0.001	57	4.6	(3.8-5.1)	114	5.1	(4.3-7.4)	0.03	39	4.6	(4.3-6.6)	133	4.9	(3.9-6.2)	0.2
C3 (UI)	17	45	(30-53)	55	82	(62-96)	<0.001	24	48	(39-93)	48	81	(63-93)	0.03	23	46	(36-92)	49	81	(62-98)	0.004
Anti-ds DNA antibodies (UI)	17	364	(123-1036)	53	35	(0-417)	0.009	27	207	(14-753)	43	72	(0-320)	0.18	22	233	(14-498)	48	33	(0-467)	0.13

Md= Median
(Q1-Q3)= Interquartile range
P= 2-tailed Mann-Whitney U test
*Includes articular, hematologic, renal, neurologic, immunologic activity or serositis

The presence of LEOL showed a moderate and mild concordance with presence of cutaneous (*k*=0.380; p<0.001) and systemic (*k*=0.228; p=0.004) activity, respectively.

The comparison of serologic values according to the presence or absence of lupus activity is shown in Table 4. We observed a higher degree of association among the serological values and the clinical findings of lupus activity corresponding to LEOL. In the individual analysis by type of clinical manifestations, higher median anti-dsDNA antibody values were observed in LE patients with articular activity (408 *vs* 82 UI; *p*=0.006) and in patients with oral erosions (449 *vs* 11 UI; *p*=0.002), oral reticular plaques (469 *vs* 77 UI; *p*=0.002) and telangiectasias (634 *vs* 72; *p*=0.02), *versus* subjects without these manifestations. We observed lower median C_3 levels in patients with articular activity (39 *vs* 80 UI; *p*=0.003), oral telangiectasias (40 *vs* 80UI; *p*=0.005), and oral ulcerative lesions (34 *vs* 79 UI; *p*=0.01) in comparison to their counterparts**.** We did not observe any other relevant associations between lupus activity and serologic tests.

LEOL did not show significant association (*i.e.*: *p*>0.003) with the rest of the analyzed variables (gender, age <40 years, type and characteristics of lupus presentation, lupus treatment, local oral factors, history of LEOL, or presence of any oral condition unrelated to LE). Oral lesions unrelated to lupus were not associated to the analyzed variables.

4. Discussion

In this study, we present the clinical, epidemiologic, and laboratory characteristics of a group of LE-patients attending our institution. The study population was predominantly Mexican *mestizo* patients currently in treatment for SLE. This study was carried out by oral pathologists in the outpatient Dermatology clinic of one of the largest referral centres for LE patients in Mexico [22].

LE is a systemic multi-organ disease with numerous manifestations which may complicate its diagnosis [23]. This fact was reflected in this study, where the diagnosis of LE took an average of six months and the amount of previously consulted physicians ranged from one to 30.

The frequency of LEOL is difficult to assess and the reported prevalences are not comparable because of the different methods used in lupus research [4]. We found that almost one fifth of our patients had LEOL, similar to what other authors have reported (20%-25%) [4,14], in contrast to other reports that range from 9 to 59% [8, 24,25].

Concerning to mouth diseases, the clinical descriptions of LEOL represent a singular problem [4,6,9,14, 26]. Details of the characteristics in LEOL are scarcely documented [4,14, 16] and there is a lack of clinical and histopathological consensus to define them [4, 27,28]. For example, LE-associated oral ulcers are defined as an "oral ulcer, usually asymptomatic, observed by the physician", which is quite unspecific [14,16] in spite of being a diagnostic criteria for SLE [29]. In the same way, specific ulcers have been described as those with classical LE histological changes (oral discoid lesions), and nonspecific ulcers in keeping with aphthous ulceration [6,30]; consequently, these ambiguous "clinicopathological" descriptions have given way to the inclusion of numerous diagnostic options [16,30]. Other LEOL not included in the American College of Rheumatology diagnostic criteria for SLE have been barely defined.

Some authors [9] detailed the clinical aspects of LEOL when lips are involved and tried to characterize their relationship with cutaneous LE-lesions [6]. In our study, we focused on all type of LEOL, we classified LEOL based on the first definitions by Schiodt [4], and the descriptions of the lesions were simplified according to the predominant clinical characteristic in order to facilitate registry and analysis. The clinical manifestations of LEOL were also detailed in our results. We considered that this data may help the clinicians to improve the detection and diagnosis of LEOL; and to acknowledge the possibility that the clinical images of LEOL may vary according to evolution, severity, and/or treatment.

In SLE, several biomarkers have been used to try to predict disease evolution or to guide therapy [31]. Certain autoantibodies have been associated with SLE-disease activity or specific clinical manifestations [32,33]; nonetheless**,** their relationship with oral mucosal lesions have been scarcely studied [34,35]. In some studies, anti-dsDNA and complement have been found to be good markers of disease activity and predictors of outcome in lupus nephritis [32, 36]. Oral ulceration has been associated with an increase in clinical activity, but has not been related to significant changes in the C3 and anti-DNA antibodies titres [35].

In our results, we observed relevant associations between LEOL and specific laboratory serum variations, such as higher levels of anti-dsDNA or lower values of C_3 in comparison to controls. These associations were observed when analyzing LEOL as a group and individually. Strikingly, not only mouth ulcers (as considered the only oral lesion in the ACR's systemic lupus classification criteria) were highly related to the studied serum variations. Noteworthy, the group of

patients with LEOL showed a higher correlation with serological markers in comparison to patients with cutaneous or systemic activity, with the exception of articular disease. In a recent study including cutaneous and systemic LE-patients [26], erosions, white reticular plaques and telangiectasias displayed associations with anti-dsDNA antibodies but no strong relationship was observed with the presence of LE-ulcers, similar to our findings [26, 35]. Further research focused on LEOL is required to allow the characterization of LEOL as a potentially useful clinical parameter in the prediction and evaluation of serologic and clinical activity in LE disease, as our results suggest. In addition, it is important to consider that anti-dsDNA antibodies have been implicated in cellular damage in SLE [37, 38], but their lack of correlation with disease activity has also been described [32].

We must underscore that clinicians must be skilled in the differential diagnosis of oral mucosal lesions in order to presume serum activity in LE patients through detection of LEOL. In this study, we also reported the prevalence of numerous mucosal findings that are not directly related to LE.

We observed a high percentage of oral candidosis, mainly the erythematous variety. LE- patients present frequently with one or several predisposing factors for the development of oral candidosis, such as the use of immunosuppressive drugs (*e.g.* steroids), antibiotics, oral prosthetics, smoking, and the immunosuppression caused by LE itself. These may explain the high frequency of observed cases in our patients. On the other hand, it is possible that in LE this clinical presentation of oral candidosis has been underdiagnosed, as it is commonly unrecognized by the physician and consequently underrated, despite its high prevalence, similar to what has been observed in HIV- infected subjects [39].

We also observed a high frequency of oral melanosis, another finding scarcely mentioned in the literature. This finding could be attributed to the ethnic characteristics of our study population [40,41]. Among Venezuelan LE patients, who are ethnically similar to the Mexican population, these lesions have been attributed to the use of antimalarials [24]. Other authors found a relationship with LE activity and pigmented macules [26], but such lesions could also be explained as a consequence of postinflammatory damage on oral mucosa. In our analysis, after adjusting for multiple variables, we did not find an association between oral melanosis and antimalarials, LE activity or smoking (data not shown). Further studies are required to determine the possible etiological factors of oral melanosis in LE patients, especially in those patients susceptible to hyperpigmentation.

An important limitation of this study was that it included only ambulatory-LE patients and few were naïve to treatment; consequently, the prevalence of LEOL could be modified. To minimize this bias, we included a considerable number of variables that potentially affect the development of oral lesions.

5. Conclusion

In this study, we present a compilation of oral lesions in patients with LE. The frequency of LEOL was high and strongly correlated with serologic disease markers, independently of cutaneous or systemic activity; although more research is mandatory in order to confirm our findings and to evaluate the potential relevance of LEOL in the follow-up and early detection of disease flares in LE patients. It would be of great value for all physicians involved in the care of LE patients to become acquainted with these lesions and their differential diagnoses, and to participate in adequately designed research to increase our knowledge regarding the pathogenesis of these lesions.

Compliance with ethical standards

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Disclosure of conflict of interest

None reported.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

Author contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: LEP, LFC, ROT, ACC and CAD. *Acquisition of data*: LEP, LFC, SMF, MFS, MJCG, MGOP, LGH and SMF. *Analysis and interpretation of data*: LEP, LFC, ROT, CAD, MFS, AHS, SMF, SPL, ACC and MSL. *Drafting of the manuscript*: LEP, SMF, LFC, ACC, CAD, SPL, MFS and MSL. *Critical revision of the manuscript for important intellectual content*: LEP, LFC, SMF, MSL, ACC, MPMG, ROT, JDC and SPL. *Administrative, technical and material support*: LEP, LFC, ACC, SMF, MSL, MFS, MJCG, LGH, MPMG, JDC and MGOP. *Study supervision*: LEP, LFC, CAD, SMF, ACC, and ROT.

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