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Oral Manifestations and Its Associated Factors in Iranian Systemic Lupus Erythematosus (SLE) Patients

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ABSTRACT

Background & Objective: Due to the overall wide range of oral manifestations and the lack of comprehensively categorized information in Iran, this study was performed to investigate the prevalence of different oral manifestations and report their possible associated factors in patients with SLE.

Materials & Methods: This cross-sectional study was performed on 96 SLE patients referred to two rheumatology clinics in Yazd, Iran, from September 2020 to February 2021. SLE patients were diagnosed based on the last revision of American College of Rheumatology (ACR) criteria in 1997. A questionnaire was created to collect demographic information and oral health status. Data were analyzed using SPSS v20.0 and p-values of $P < 0.05$ were considered statistically significant.

Results: This study included 13 men (13.5%) and 83 women (86.5%), with an average age of 31.9 ±11.35 years. Oral lesions were diagnosed in 64.4% of patients, with white and red lesions being the most frequent (58%), and the most common region involved was buccal mucosa (25.8%). 97.1% of participants had caries and 86.5% had periodontal diseases. There was a significant association between the presence of oral lesions and female gender, longer duration and higher activity level of the disease and simultaneous presence of periodontal disease and missing or filled teeth. ($P < 0.05$).

Conclusion: Given the frequency of oral lesions in more than 60% of patients, as well as the high incidence of caries and periodontal disorders, regular oral examinations in these patients appear to be particularly important.

Keywords: Oral health, Oral lesions, Lupus Erythematosus

Introduction

Mucosal involvement is prevalent in lupus patients, but since 1997, only ulceration has been expressly included in the American College of Rheumatology (ACR) criteria for systemic lupus erythematosus (SLE), and less emphasis has been paid to the remainder of the oral manifestations associated with lupus. (1-3). SLE oral lesions were detected in 5-25% of cases, with some studies indicating rates as high as 80% (4). The clinical descriptions of oral lupus lesions vary considerably between studies and the terminology used to describe oral lesions in the previous literature is sometimes ambiguous. Some of the unspecified terms used are as follows: oral ulceration, honeycomb plaque, keratotic plaque, nonspecific erythema, and purpura (5, 6). As the classification of oral manifestations is inconsistent and the clinical descriptions of the lesions are not meticulous, it is practically difficult to summarize previous studies on the prevalence of various oral lesions in lupus. Other oral problems that are more common in this group of patients than in the general population are mentioned below.

Both xerostomia and hyposalivation predispose these patients to dental caries as well as recurrent non-infectious pharyngitis. Because of the use of corticosteroids for the treatment of SLE, oral candidiasis and other opportunistic infections are also prevalent (5). Gingivitis and periodontitis have also been shown to be more prevalent in SLE cases (7). Previous articles have listed several reasons why health care providers, including physicians and dentists, should pay attention to oral manifestations in patients with lupus and take the time to examine and treat them. Diagnosis and treatment of some oral problems such as periodontal diseases may reduce SLE activity level according to some evidence and therefore make the overall management of lupus easier (8, 9). Other head and neck infections should also be monitored to prevent

further development of possible infections in other parts of the body caused by long-term immunosuppressive therapy in these patients (10). Some research has revealed that oral lesions may take precedence over other symptoms and can be used to diagnose lupus. The emergence of oral symptoms in lupus patients has been regarded as a warning sign that patients are entering a phase of increased disease activity (11, 12). Oral ulcers, especially when they become chronic in SLE, pose a risk of developing squamous cell carcinoma. Therefore, it is recommended that a biopsy be performed as soon as possible when the diagnosis is not definitive or the lesions appear to have no improvement. So it is another important reason why the diagnosis and treatment of these lesions should not be delayed (13).

Genetic factors, geographical variations and socioeconomic patterns appear to play an important role in overall manifestations and outcomes of SLE (14, 15) and according to the scarcity of data from Iran, and especially in Yazd province, and considering the importance of oral examination in this group of patients based on all the above reasons, this study aimed to assess the prevalence of oral manifestations in SLE Iranian patients categorized by their types and regions, and their possible association with age, gender, the activity of the disease, and disease duration.

Materials and Methods

Study design

From September 2020 to February 2021, 96 patients with systemic lupus erythematosus were referred to two rheumatology clinics in Yazd, Iran: Shahid Sadoughi and Shahid Rahnemoun.. Patients has been diagnosed with SLE using ACR criteria (14, 15). Patients' informed consent to participate in the study and their capacity to tolerate oral and dental examination procedures were the inclusion criteria for the study. All patients who met the inclusion criteria were enrolled in the study by the census. Patients who were pregnant or had underlying systemic diseases other than lupus were excluded.

The patients were initially assessed by our rheumatologist and then referred to our post-graduate dentistry student for an oral and dental examination. The personal characteristics of each SLE patient, including demographic information (age, gender), duration of the disease, activity status based on clinical and serological data, and type of medications used, were all recorded using a questionnaire. The rheumatologist used the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) criteria to determine whether a patient was in the active or inactive phases of the disease (16). A SLEDAI index cut-off of greater than four was considered as the presence of active disease. Then the patient's intraoral examination was done with a mirror under appropriate light.

Oral examination

Oral lesions were clinically evaluated and categorized based on their morphologic characteristics and location. The following locations were examined: hard palate, soft palate, lips (including upper and lower), commissure of lips, tongue, buccal mucosa, and vestibular depth of both jaws. Oral mucosa lesions were first recorded in four major categories (3), which include: 1. Ulcerative lesions 2. White and red lesions 3. Pigmented lesions and 4. Exophytic lesions. In this classification, the appearance of oral lesions was examined and no histological or laboratory evaluation was considered (3). Then, a comprehensive clinical description of the oral manifestations of SLE was reported, which can be contained into different subgroups of this classification, including petechiae, cheilitis, candidiasis, and herpetic lesion. Our oral medicine specialist confirmed the diagnosis of lesions.

Decayed, filled, and missing teeth were also recorded in these patients. The health status of the periodontium is also assessed by examining the appearance factors of the gingiva (such as color, contour, and consistency), measuring the probing depth and examining the bleeding on probing by the Williams probe, determining the amount of clinical attachment loss, and evaluating the mobility of teeth. Then periodontal status was reported as healthy, gingivitis or periodontitis according to the 2017 world workshop on the classification of periodontal and peri-implant disease and conditions (17).

Ethical considerations

The ethical committee of Shahid Sadoughi University of Medical Sciences approved this cross-sectional study (IR.SSU.REC.1398.099). After a thorough description of the nature and aim of the study, the subjects provided written informed consent. This study was performed in accordance with the Declaration of Helsinki and subsequent revisions.

It should be noted that the patient did not pay extra for the serological data needed to calculate disease activity, and the preparation of these tests was part of the lupus control process. After performing oral examinations in case of these lesions, patient has been informed of the possible problem and the necessary recommendations have been given to the patients to treat and follow these lesions.

Statistical analysis

Descriptive statistics, including frequency distributions for discrete variables, and mean (standard deviation) for continuous variables, were calculated for all outcome variables. The collected data was analyzed using SPSS version 20 software, the Chi-square test, Fishers' Exact tests, and the logistic regression model. P-values less than 0.05 were considered significant.

Results

In this study of 96 SLE patients, 13 men (13.5%) and 83 women (86.5%) with ages ranging from 17 to 69 years and a mean of 31.9±11.35 years were divided into three groups: 15-30, 30-49, and over 49.

Oral lesions were seen in 62 (64.4%) SLE patients. The age group over 49 years had the highest incidence of lesions, although statistical analysis revealed no significant association between age and the presence of oral lesions (P-value = 0.9) (Table 1).

Table 1. The distribution of SLE patients based on oral lesions and other variables

Variables		Oral lesion				P value
		With lesions		Without lesions		
		Number	%	Number	%	
Gender	Male	4	30.8	9	69.2	0.011*
	Female	58	69.9	25	30.1	
Age in years	15-30	32	62.7	19	37.3	
	31-49	21	65.6	11	34.4	0.952
	50 and above	6	66.7	3	33.3	
SLE duration	Less than 8 years	38	56.7	29	43.3	0.014*
	More than 8 years	24	82.8	5	17.2	
SLE activity	Active	17	18	4	19	0.004*
	Inactive	20	46.5	23	53.5	
	Unknown	25	78.1	7	21.9	
Medications	Corticosteroids	3	37.5	5	62.5	0.284
	Anti-malarial	9	75	3	25	
	Corticosteroids+ antimalarial	30	62.5	18	37.5	
	Corticosteroids+ antimalarial+ immunosuppressive	20	71.4	8	28.6	
Periodontal status	Normal	1	7.7	12	92.3	0.001*
	Gingivitis	29	74.4	10	25.6	
	Periodontitis	32	72.7	12	27.3	
Dental status	Caries	57	64.8	31	35.2	1.00
	Filled teeth	38	56.7	29	43.3	0.014*
	Missing teeth	30	54.5	25	45.5	0.017*

Chi-square and Fishers' Exact tests, P=0.00, P<0.05 – Statistically significant. P – Probability value

67 SLE patients (69.8%) had a disease duration of fewer than 8 years, while 29 patients (30.2%) had a disease duration of more than 8 years. Furthermore, the status of disease activity was active in 21 patients (21.9%), inactive in 43 patients (44.8%), and unknown in 32 patients (33.3%) due to a lack of updated serological information needed for the calculation of the SLEDAI criteria.

Out of 62 diagnosed oral lesions, the most common were white and red lesions (58%), each ulcerative and pigmented lesion had 12 cases (19.4%), and the lowest manifestation was related to Exophytic lesions (3.2%). During the evaluation of the frequency of the lesion subgroups, there were 15 cases (31.9%) of cheilitis, which was the most common one, then candidiasis and petechiae, each with 12 cases (25.5%), and the lowest prevalence was related to herpetic lesions (17%).

Furthermore, the frequency of lesions regions was reported as follows: buccal mucosa (25.8%), commissure of lips (24.2%), hard palate (12.9%), soft palate (11.3%), maxillary vestibule depth (9.7%), upper lip (8.1%), lower lip (4.8%) and tongue (3.2%), respectively.

Periodontitis was found in 44 patients (45.8%), gingivitis in 39 patients (40.6%), and healthy

periodontium in 13 patients (13.5%). During the assessment of dental health status, 88 cases (91.7%) had caries, 67 cases (69.8%) had filled teeth and 55 cases (57.3%) had missing teeth.

Using the Chi-square and Fishers' Exact tests, it was found that six variables have a statistically significant association ($P < 0.05$) with the presence of oral lesions: Sex, duration of disease, disease activity status, periodontium status, filled teeth, and missing teeth. However, there was no significant association between age, medication type, or active caries and the prevalence of oral lesions ($P > 0.05$) (Table 1).

The results of logistic regression analysis revealed that the probability of occurrence of oral lesions in males was 91% lower than in females. The probability of occurrence of oral lesions at the age of 50 and above was 95% lower than in younger ones. With an SLE duration of more than 8 years, the risk of oral lesions is 33.75 times more than with an SLE duration of fewer than 8 years. In the inactive phase of SLE patients, the probability of oral lesions was 96% lower than in the active phase. The presence of oral lesions in SLE patients who took anti-malarial medicines alone was 38.3 times more than in those who used corticosteroids alone. Gingivitis (OR = 177) and periodontitis (OR = 120) significantly increased the probability of simultaneous presence of oral lesions compared to healthy conditions ($P < 0.05$) (Table 2).

Table 2. Evaluation of related factors to the possibility of oral lesions in SLE patients using logistic regression

Variables			Odds Ratio	P value	[95% Conf. Interval]
Gender	Female		1	-	-
	Male		0.098	0.043*	0.01-0.93
Age in years	15-30		1	-	-
	31-49		0.7	0.74	0.08-5.73
	50 and above		0.05	0.03*	0-0.77
SLE duration	Less than 8 years		1	-	-
	More than 8 years		33.7	0.005*	2.81-404.77
SLE activity	Active		1	-	-
	Inactive		0.043	0.004*	0.005-0.35
	Unknown		0.49	0.498	0.06-3.79
Medications	Corticosteroids		1	-	-
	Anti-malarial		38.34	0.021*	1.74-840.4
	Corticosteroids+ antimalarial		10.42	0.045*	1.04-103.7
	Corticosteroids+ antimalarial+ immunosuppressive		5.91	0.156	0.50-68.97
Periodontal status	Normal		1	-	-
	Gingivitis		177.06	0.014	2.79-11209.14
	Periodontitis		120.04	0.028*	1.66-8666.57
Dental status	Caries	Yes	1	-	-
		No	21.156	0.06	0.830-539.03
	Filled teeth	Yes	1	-	-
		No	0.872	0.88	0.149-5.09
	Missing teeth	Yes	1	-	-
		No	4.20	0.139	0.086-5.73

Logistic regression analysis, P=0.00, P<0.05 – Statistically significant. P – Probability value, confidence interval

Discussion

In our study, the mean age of the 96 SLE patients was 31.90 ± 11.35 years, and the majority of patients (86.5%) were female. Many studies have shown that the disease is more common in women (18, 19). The female-to-male ratio in this study was 6.5:1, which is similar to the ratio reported in another Iranian study in Fars province in 2008 by Nazarinia (20). Higher female-to-male ratios were reported in the studies of Hammoudeh in Qatar (9.5:1) and China (9.6:1) (10, 21). Furthermore, the mean age of participants in our study was fairly near to some studies (22, 23). For example, in Del Barrio's study, the average age of patients was stated to be 38.31 ± 10.65 years or about 30.27 years in Nazarinia's study, but Rezvaninejad et al reported a higher mean age of 42.9 ± 6.1 years in a recent study in Bandar Abbas (6, 20, 24).

In the current study, 64.4% of SLE patients had oral lesions, which was similar to the study done by Zakeri in Zahedan (61.4%) (23). In contrast, the prevalence of oral lesions in our study was higher than in Villamin's study in the Philippines (33%) (25). According to Brennan's review, the prevalence of oral mucosal lesions in SLE patients ranged from 2-80%, with a mean of 20-30% (26). De Rossi's review, on the other hand, revealed that the frequency of oral lesions in SLE patients was 81.3–87.5%. The differences could be related to a lack of commonality in the types of lesions investigated in De Rossi's review (27).

In our study, oral lesions were diagnosed in 64.4% of patients, with white and red lesions being the most frequent (58%), and the most common regions involved were the buccal mucosa (25.8%). The majority of lesions in Lourenço's study were lichenoid lesions, with the lips and buccal mucosa being the most affected areas (28).In contrast to our study, the most prevalent oral lesions in both Khatibi's study in Tehran and Rezvaninejad's study in Bandar Abbas were ulcers, but the most common sites remained the buccal/labial mucosa and lips, respectively (24, 29). The lower prevalence of ulcers among our participants could be attributable to fewer selected patients having active SLE at the time of the investigation. The Zakeri study found that the most prevalent oral lesions were white and red lesions (56.13%), which was similar to our findings, but the most common site of their lesions was in the soft palate, which contradicted our findings (23). According to our study, the rate of pigmented lesions was 19.4%, while in Chacón-Dulcey's study in Venezuela, 9.5% of SLE patients had multiple hyper-pigmented macules in the buccal mucosa (18).

In our study, the prevalence of chillitis was 31.9%, candidiasis 25.5%, petechiae 25.5%, and herpetic lesions 17%. Cheilitis and candidiasis were observed in 2.4% of SLE patients in Hammoudeh's study, while petechiae were found in 16.7%, which differed from our results (10). Other findings also show that SLE patients had a higher prevalence of herpetic lesions as a result of immune dysregulation and immunosuppression (30). Oral candidiasis is a frequent problem in SLE patients, according to Leite et al., who reported a much greater frequency than our study (54% versus 25.5%) (31).

One of the side effects of SLE is the development of gingivitis and periodontitis, which directly affect the tooth support structures. In this study, by examining the status of the periodontium in SLE patients, the prevalence of gingivitis and periodontitis was 40.6% and 45.8%, respectively.

While a study in the United Kingdom revealed a greater frequency of periodontitis in SLE patients (85%), the Hammoudeh study found a prevalence of gingivitis and periodontitis of 54.8% and 57.1%, respectively, which is virtually equivalent to our findings (10, 32).

The frequency of decayed, filled, and missing teeth in our study was 91.7%, 69.8%, and 57.3%, respectively. These findings are consistent with previous research, such as the Gofur study, which discovered that 74% of Indonesian patients had decayed teeth, 66% had missing teeth, and 60% had filled teeth (33). In a study conducted by Hammoudeh et al. in Qatar, the prevalence of caries was 88.1%, while the frequency of missing teeth was 64.3% (10). A large number of cariogenic bacteria (Streptococcus sobrinus and Streptococcus mutans) have been foundin supragingival plaque samples from patients with SLE. It seems that lowering both the pH and the flow rate of saliva increases the risk of tooth decay in these patients (34).

In our study, statistical analysis revealed a significant association between the prevalence of oral lesions in SLE patients with female gender, longer SLE duration, higher disease activity, simultaneous presence of periodontal diseases, and the incidence of filled and missing teeth ($P < 0.05$). However, the association between age, medication type, and caries with oral lesions was not significant ($P > 0.05$). We would add that there was no comparison with all these variables because there were a limited number of previous studies that listed these related factors, and there was no single study that addressed all of these variables together. There was no significant relationship between the prevalence of oral lesions and gender, age, or disease duration in Zakeri's study (23). In Khatibi's study, age and gender had also no statistically significant association with oral lesions (29). Rezvaninejad, on the other hand, found significant associations with both female sex and being over 45 years old, which was somewhat similar to our findings (24).

In the study of Khatibi, there was a significant association between the presence of oral lesions and SLE duration, daily intake of corticosteroids, and medications used to treat SLE other than corticosteroids **(29)**. According to logistic regression, the presence of oral lesions in SLE patients who took anti-malarial medicines alone was 38.3 times more than in those who used corticosteroids alone. . This may be explained by the fact that antimalarial drugs are mainly effective in reducing oral lesions, and one of the reasons for their prescription is the treatment of oral ulcers, especially those that were not managed by corticosteroids, so perhaps this is the reason for this difference **(13)**.

Interestingly, in conversations with patients, most of them were unaware of the presence of lesions in their oral cavity. As mentioned before, oral lesions were associated with greater disease activity index (SLEDAI) levels in this research ($P < 0.05$) in contrast to the Kudsi's study **(35)** but in agreement with Del Barrio and Aurlene's studies **(6, 22)**. It seems that we need to be more vigilant about the periodic evaluation of oral lesions, especially those that are not associated with significant discomfort in patients. In addition, the type of ulcers among lesions may undergo malignant changes if left untreated **(13)**. Apart from that, oral lesions may be one of the first symptoms of a systemic underlying disorder such as lupus, so physicians and dentists should pay special attention to oral examination in patients with non-specific complaints, and inform patients of the importance of treatment if oral lesions are found. In this way, they will take an important step toward early either diagnosis or controlling of lupus, as well as avoid aggressive tests, increased costs, and incorrect therapeutic choices.

Since the link between skin lesions and the occurrence of some potentially life-threatening complications, such as lupus nephritis, has been established in numerous studies, research into the link between oral lesions and other systemic manifestations, particularly skin lesions, may be useful in predicting the course of the disease **(36, 37)**. Although future longitudinal studies are required to determine causal links with all associated factors.

Conclusion

Given the prevalence of oral lesions in more than 60% of patients, as well as the high prevalence of caries and periodontal problems, regular oral examinations of these patients appear to be more important.

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Conflict of Interest

Authors declare no conflict of interests.

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