ORIGINAL ARTICLE

Oral and Systemic Manifestations of Systemic Lupus Erythematosus; Exploring the Association

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OBJECTIVE: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with variety of clinical and oral mucosal presentations. Our study aimed to record all those oral pathological changes which occur in patients of SLE and observe the associations between the clinical signs and oral disease status.
METHODOLOGY: Present study was conducted in Rheumatology Department of Shaikh Zayed Medical Complex, Lahore, Pakistan. Consecutive sampling was done, and 130 diagnosed patients with SLE of both genders and all ages were recruited in the study after getting written informed consent. Patients with any comorbid conditions were excluded from the study. Detailed clinical and oral examinations were performed, and relevant disease findings were recorded. Associations between oral and clinical manifestations were computed through chi-squared test of significance keeping the confidence level at 95%.
RESULTS: Out of 130 patients, 115 were females and 15 were males. Mean age of patients reported with SLE was 31.65 ± 9.5 years. Arthritis was the most common clinical finding followed by photosensitivity. Among the oral pathologies, oral ulcers, xerostomia, gingivitis, glossitis, mucositis, gingival bleeding, and hyperplasia were observed. Nephritis was associated with most oral manifestations, followed by psychosis, hair loss and skin rash.
CONCLUSIONS: SLE has a strong component of oral mucosal pathologies. The most common skin findings were rash, followed by photosensitivity and arthritis. Commonest oral manifestation was oral ulceration present and past. Significant associations were found between certain oral and systemic manifestations.
KEYWORDS: Systemic Lupus Erythematosus, Systemic, Oral, Ulcer.
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INTRODUCTION

Systemic lupus erythematosus (SLE) is the multisystem autoimmune disease with a broad spectrum of clinical manifestations that involve almost all organs and tissues of the body. It is characterized under autoimmune disease, in which the patient's immune system attacks its own body tissues, especially the cellular nuclei or its components.[1] The geoepidemiology of SLE demonstrates ethnic differences which are largely due to genetic susceptibility and environmental factors.[2] Risk of developing SLE is great among non-white people especially South Asian and East Asian countries where the prevalence rate of SLE is between 30 to 50 per 100,000.[3]

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Disease is caused by a complex interaction between different genetic, hormonal, epigenetic and environmental factors. Overload of immune complexes in the form of nuclear autoantigens and uncontrolled production of IFN-Alpha are the hallmarks.[4] However, complete pathogenesis of SLE is still not clearly understood. SLE belongs to the group of diseases which show immense diversity in its clinical parameters.[5-7] Patients report broad variety of symptoms some are representative while others are constitutional features of disease both systemic and oral.[8,9]

Pakistan has relatively younger lupus patients as compared to other countries.[10] Understanding about oral pathological spectrum is necessary because early detection of oral mucosal changes may help in starting treatment early leading to decrease disease morbidity and improved quality of life. The aim of this study is to present the spectrum of oral mucosal pathologies of SLE and record if there are any associations between oral and systemic manifestations of disease in these patients.

METHODOLOGY

This descriptive study has been conducted in division of Rheumatology, Sheikh Zayed Hospital Lahore, in collaboration with Department of Oral Pathology, Department of Morbid Anatomy & Histopathology and Department of Immunology University of Health Sciences Lahore. Consecutive sampling was done, and 130 diagnosed patients of both genders and all ages were recruited in the study after getting written informed consent. Patients with any comorbid condition were excluded from the study. General physical examination involving detailed clinical evaluation of the disease was done under supervision of concerned medical specialist and relevant disease findings were recorded. Intra-oral examination was performed under proper illumination with the help of dental mirror and probe. Oral mucosal changes from erythema to ulceration in any part of the mouth at the time of examination were recorded.

Sizes of oral ulcers (in mm) and their numbers were recorded in questionnaire. Periodontal changes of the diseases were evaluated according to basic periodontal examination guidelines by British Society of Periodontology (BSP) (Dietrich et al., 2019). In addition, the gingival assessment was performed by Silness-Loe index (Nimbulkar et al., 2020). Subjective xerostomia was evaluated through a question "Does your mouth usually feel dry?" using a dichotomous response technique including 'YES' or 'No' responses (Fleming et al., 2020). Above mentioned clinical examination was supported by evident history findings and recorded for each study participants.

The current study was approved by ethical review committee of University of Health sciences Lahore, Pakistan vide letter number UHS/REG-17/ERC/4382.

STATISTICAL ANALYSIS

Data was coded analyzed using IBM SPSS Version: 25.0. Mean and standard deviation was calculated for age of patient, number of oral ulcers and their sizes. Frequency and percentage were calculated for gender and stage of disease. The associations between oral and clinical manifestations was done using chi-square test of significance. For all analysis, a p-value of ≤ 0.05 was considered as statistically significant with a confidence level of 95%.

RESULTS

Out of 130 patients, 115 were females and 15 were males highlighting a significant female predominance. Mean age of patients reported with SLE was 31.65 ± 9.5. Family history of SLE was positive in 28 patients. 59% of patients presented with moderate stage of disease while 32% had mild stage and only 9% had severe stage of SLE.

On clinical examination Arthritis was present in 96.9 % of patients while photosensitivity in 87%. These two clinical findings were present in every spectrum of disease. On the other hand, CNS involvement in the form of seizures or psychosis was present only 18 patients with severe disease manifestations. Malar rash was present in 78%, skin rash in 67%, nephritis in 42% while cardiac problems were present in 37% (Table-1).

Table-1: Clinical Findings in SLE Patients

Sr. No	Clinical Findings	Numbers	Percentages
1.	Malar Rash	102	78.5%
2.	Skin Rash	88	67.7%
3.	Photosensitivity	114	87.7%
4.	Arthritis	126	96.9%
5.	Nephritis	55	42.3%
6.	Respiratory or Cardiac Problems	48	36.9%
7.	Seizures or Psychosis	18	13.8%
8.	Hair Loss	68	52.3%
9.	Weight Loss	51	39.2%

On oral examination oral ulcers were present in 39.2 % while 80% of the patients gave history of oral ulcerations which were present at certain point of their disease progression but now had been healed at the time of their oral examination. Xerostomia was present in 69% of patients while gingivitis in 59%, gingival bleeding in 38%, gingival hyperplasia in 18%, mucositis in 42% and glossitis was present in 43% of patients (Table-2).

Table-2**:** Intra-oral Findings in SLE Patients

Sr. No	Intra-Oral Findings	Numbers	Percentages
1.	Oral Ulcers	59	39.2%
2.	History of Oral ulcers	104	80%
3.	Gingivitis	77	59.2%
4.	Gingival Bleeding	49	37.7%
5.	Gingival Hyperplasia	23	17.7%
6.	Periodontitis	39	30%
7.	Mucositis	55	42.3%
8.	Glossitis	56	43.1%
9.	Xerostomia	90	69.2%

Statistical associations were computed among oral and systemic manifestations of the disease and as shown in Table 3, significant association was observed between oral mucosal changes with the systemic conditions of nephritis, psychosis, hair loss and skin rash.

Table-3: Association of oral and systemic manifestations of SLE

Oral manifestations of SLE	Clinical manifestations of SLE								
	Malar Rash	Skin Rash	Photosen -sitivity	Arthritis	Nephritis	Seizures/ Psychosis	Hair Loss	Weight Loss	Respirat ory or Cardiac Problems
Gingival Bleeding	p= 0.49	p= 0.27	p= 0.27	p= 0.59	p= 0.92	p= 0.91	p= 0.01*	p= 0.41	p= 0.68
Gingival Hyperplasia	p= 0.97	p= 0.09	p= 0.90	p= 0.69	p= 0.04*	p= 0.43	p= 0.36	p= 0.16	p= 0.81
Mucositis	p= 0.94	p= 0.29	p= 0.50	p= 0.08	p= 0.53	p= 0.22	p= 0.42	p= o.60	p= 0.53
Glossitis	p= 0.97	p= 0.24	p= 0.95	p= 0.45	p= 0.02*	p= 0.24	p= 0.04*	p= 0.27	p= 0.39
Gingivitis	p= 0.60	p= 0.09	p= 0.93	p= 0.79	p= 0.20	p= 0.001*	p= 0.88	p= 0.74	p= 0.80
Periodontitis	p= 0.78	p= 0.28	p= 0.29	p= 0.82	p= 0.004*	p= 0.74	p= 0.16	p= 0.29	p= 0.52
Xerostomia	p= 0.45	p= 0.70	p= 0.59	p= 0.17	p= 0.26	p= 0.05*	p= 0.72	p= 0.78	p= 0.13
Oral Ulcers	p= 0.38	p= 0.33	p= 0.07	p= 0.65	p= 0.04*	p= 0.62	p= 0.40	p= 0.71	p= 0.23
History of Oral Ulcers	p= 0.74	p= 0.03*	p= 0.59	p= 0.80	p= 0.99	p= 0.09	p= 0.42	p= 0.59	p= 0.78

*Statistically Significant

DISCUSSION

SLE being a multisystemic autoimmune disease has gained primary attention in current era all over the world where abundant pollutants and genotoxic agents are present to derange the life and life care systems. In current study, we have tried to understand the wide spectrum of oral diseases present in SLE along with other clinical variables. Systemic lupus erythematosus exhibits sexual dimorphism, being more common in females than in males. Out of 130 patients who were included in our research, 115 were females and only 15 were males. These results are in accordance with the previous studies in Pakistan.[11] Similar findings were observed by Rabbani and colleagues from Karachi.[12] Another study in U.S suggested the similar picture about gender distribution of disease which was nine times more common in females as compared to males. It was observed that the acquisition of SLE is highly gender bias in which presence of 'X' chromosome, the hormonal makeup, the female sex steroid; estradiol and its receptor chemistry can explain the etiology but the underlying mechanisms are still enigmatic.[5]

In present study, mean age of patients reported with SLE was 31.65 ± 9.5 years. A local study in Karachi, Pakistan, by Rabbani and colleagues also reported the mean age of SLE patient being 31 years.[12]. It is important to note that most of the patients belongs to childbearing age. So, this is not a disease of geriatric population.

Family history in term of patient's first-degree relatives was positive in 21.5% of patients. Similar findings were observed in a study conducted in Italy reported 22.7% of patients who had positive family history of SLE.[13] Presence of disease in family is a potential risk factor for a person to develop SLE during some part of his/her life. Its justification lies in a fact that disease susceptible genes runs in succeeding generations, environmental triggers may play a role which might result in differences in various populations.[14]

Regarding clinical manifestations, arthritis was found to be the commonest sign followed by photosensitivity followed by other clinical manifestations. Another study in Lahore, Pakistan shows similar findings as photosensitivity (60%), malar rash (60%) and skin lesions (58%).[15] A study conducted in Karachi, Pakistan reported malar rash (29%), photosensitivity (6%), arthritis in (38%) and seizures or psychosis in 14% of patients.[12] Study in Saudi Arabia reported 624 SLE patients in which arthritis was present in 80.4%, malar rash (48%), nephritis (47.9%), neuropsychiatric manifestations were 27.6%.[16] While a study in U.S reported nephritis in 37% of SLE patients. Above minor differences in different populations might be due to inter-ethnic variations and genetic differences.

Complete intra-oral examination was performed for 130 patients included in our study. Oral ulcers, the pathognomonic for SLE were present in 39% of patients at the time of clinical examination. History of presence of oral ulceration during any part of disease course in patients was consistent finding which was present in 80% of patients. Another important finding was presence of xerostomia or dryness of mouth which was present in 69% of patients and most of them belong to geriatric population. Similar findings were observed in a study conducted in Brazil which showed 58% of the patients reported with xerostomia due to immune attack on salivary glandular parenchyma.[17] Gingivitis was observed in 59% of patients while glossitis and mucositis were observed in 43% and 42% of patients respectively. 17% of patients who were using cyclosporine reported gingival hyperplasia.

Cyclosporine drugs used as an immunosuppressant in SLE patients stimulate gingival fibroblast which results in unusual gingival overgrowth.[18] Oral findings reported in other studies include mucositis, gingivitis, angular cheilitis, dry mouth, dental caries, hypogeusia, dysgeusia, glossodynia and burning sensation of mouth. Xerostomia is reported to be present in almost all patients of SLE while periodontitis has been observed in 93.8% of the patients.[19] As Hyposalivation increases the chances of dental caries and extensive tooth decay, apart from this mucosa becomes susceptible to mechanical injuries leading to non-infectious mucositis and pharyngitis.

Oral health in SLE in intimately connected with the overall health of patient. Most of the time oral health evaluation creates a window of understanding about the systemic health issues of SLE patients. A significant link was observed between some oral and systemic manifestations of SLE which support the concept of oral-systemic health connection. Significant association was observed between

nephritis and many oral manifestations of SLE like gingivitis, oral ulcers, gingival hyperplasia, and glossitis. The increased systemic inflammatory burden in chronic renal disease potentiates the proinflammatory cascades of SLE and ultimately results in vasculitis and gingival inflammation.[20] Vasculitis of Lupus is far away different from normal vasculitis in terms of targeting medium and small sized blood vessels especially without involving large sized vessels. As a consequence; involvement of oral mucosa in the form of gingivitis, glossitis and oral ulcerations co-manifest with nephritis and other systemic vasculitis.[21]

Cutaneous involvement of SLE in the form of skin rash was found to be significantly associated with history of oral ulceration. Vascular attack by abnormal immune complexes formed in SLE disintegrate the epithelium of skin, gingival tissue, and oral mucosa resulting in ulcerations.[22] The body-wise inflammation in Lupus affects the skin and its appendages leading to in destruction of hair follicles which depicts as alopecia or thinning of hair.[23] Similar finding was observed in our study in which a significant link was observed between hair loss and glossitis or mucositis.

Another significant association in our study was observed between seizures and gingival inflammation or gingivitis. Here we can observe the gingivitis as a disease; involving those patients with SLE complications and involvement of vital organs like CNS or gingivitis as a condition; depicting plethora of problems in patients who are unable to maintain oral hygiene in episodes of seizures. In both situations an evident need is present to deal the SLE manifestations as a whole, without fractioning the systemic problems and treating them individually. Maintenance of meticulous oral hygiene is helpful in treating the oral conditions which usually fade out under the blanket of systemic problems.

CONCLUSION

The patients examined had significant oral manifestations along with and skin manifestations. The most common skin findings were arthritis, followed by photosensitivity and rash. Commonest oral manifestation was history of oral ulceration xerostomia and gingivitis. Significant associations were found between certain oral and systemic manifestations that need to be further evaluated in future investigations. Understanding about oral pathological spectrum is necessary because early detection of oral mucosal changes may help in designing treatment therapy thus, lessening the disease burden and improving the quality of life.

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CONFLICT OF INTEREST

None declared

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