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Oral lesions of systemic lupus erythematosus: A collaborative Latin American study

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Abstract

Background: Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease that may affect the oral mucosa. The variable spectrum of oral lesions observed in SLE can pose challenges in diagnosis, particularly when the lesions occur in isolation. The aim of this study was to describe the oral lesions occurring in patients with SLE from Latin America.
Methods: This collaborative record-based study involving 11 oral and maxillofacial pathology and medicine services across Venezuela, Argentina, Chile, Brazil, and Mexico describes the clinicopathological profile of SLE-related oral lesions.
Results: Seventy patients with SLE and oral lesions were included in the study. The majority were females (75.7%; female/male ratio: 3.1:1) and white (62.1%), with a mean age of 38.4 years (range: 11–77 years). The most common site of oral lesions was the hard/soft palate (32.0%). Clinically, oral lesions predominantly presented as ulcers (26.6%), erosions (26.6%), and white lesions (23.4%). Isolated oral lesions occurred in 65.2% of individuals, while cutaneous manifestations occurred in 80.3%. The main clinical diagnostic hypothesis in 71.4% of cases was an immune-mediated disease. Oral biopsies followed by histopathological analysis were performed in 50 cases.
Conclusion: Oral lesions of SLE exhibit a variety of clinical and histopathological features. A key point in diagnosis is that unusual oral changes without an obvious local cause may indicate a possible systemic condition presenting with oral lesions. A multidisciplinary approach, which includes regular oral examination, is warranted to identify oral lesions and provide treatment.

Keywords

Autoimmune disease, differential diagnosis, Latin America, oral mucosa, systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with diverse clinical manifestations that can potentially lead to severe organ complications and even death.[1] The disease is characterized by loss of self-tolerance and the formation of nuclear autoantigens and immune complexes.[2,3] The incidence and rate of newly diagnosed SLE populations are estimated at 5.14 per 100,000 person-years and 0.4 million people annually, respectively.[4]

Orofacial lesions are quite common among individuals with SLE[5–7] and are part of the set of criteria established for diagnosing the disease.[8] The prevalence of these lesions varies depending on the treatment received and disease activity.[7,9] Recent literature has described that oral lesions occur in more than 40% of individuals with SLE[6] and, in some instances, the diagnosis can be challenging, particularly if the lesion occurs in isolation.[6,10] Some authors have highlighted that the 'oral ulcers' terminology used in the current SLE diagnostic and classification panel is often vague and poorly defined.[5,11] This is because clinically there is a variable spectrum of oral lesions in SLE, which can mimic other groups of diseases. Thus, unusual oral lesions without an obvious local cause may alert clinicians to a possible SLE that presents secondarily with oral symptoms.[5,6]

SLE-related oral lesions have been previously described in reports from Brazil;[6,7] however, information about specific oral lesions of SLE in other Latin American countries has been barely documented. The purpose of the present collaborative study was to report the clinicopathological features of oral lesions in patients with SLE diagnosed at 11 referral services in Venezuela, Argentina, Chile, Brazil, and Mexico.

Materials and methods

Study design, sample, and ethical issues

This case series comprised 70 individuals with SLE-associated oral lesions, whose records were retrieved from the archives of 11 oral and maxillofacial pathology and medicine services across five Latin American countries. The following centers participated in the study: Universidad Central de Venezuela, Caracas, Venezuela ($n = 39$), Hospital Señor del Milagro Salta, Salta, Argentina ($n = 11$), Universidad Nacional de Córdoba, Córdoba, Argentina ($n = 2$), Universidade Federal de Goiás, Goiânia, Brazil ($n = 3$), Universidade de São Paulo, São Paulo, Brazil ($n = 2$), Universidade Estadual da Paraíba, Campina Grande, Brazil ($n = 2$), Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil ($n = 1$), Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil ($n = 1$), Private clinic MedOral SF, San Luís Potosí, Mexico ($n = 5$), Universidad Andrés Bello, Viña del Mar, Chile ($n = 3$), and Universidad de Valparaíso, Valparaíso, Chile ($n = 1$). The study was reported following the strengthening the reporting of observational studies in epidemiology (STROBE) checklist.[12] Authorization was obtained from each participating institution, and ethical approval was granted by the Research

Ethics Committee of Universidade Federal do Rio de Janeiro (No. 5481602). The study was conducted in accordance with the Declaration of Helsinki and written informed consent was obtained from all participants.

Diagnostic criteria

Individuals diagnosed with SLE according to the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for SLE[8] were included. General manifestations and presence of mucocutaneous features, i.e., malar rash, generalized rash, and discoid rash were also parameters considered in the inclusion criteria.[8] Clinically, oral lesions were considered to be isolated or multiple, with the appearance of ulcers, erosion, erythema, white lesion, macule, bulla, crust, and desquamative gingivitis.[5]

An oral biopsy was also obtained as an additional diagnostic approach in 50 cases. These individuals underwent an incisional biopsy, which was indicated to rule out neoplasms, infections, or other immune-mediated diseases. In 20 patients with oral lesions, the diagnosis of SLE had been previously made by rheumatologists and/or dermatologists who were involved in monitoring disease activity, and no oral biopsies were performed. Histological evaluation with hematoxylin and eosin and periodic acid-Schiff (PAS) was performed. The following histologic features were considered: a generally atrophic epithelium, vacuolization of keratinocytes, edema in the upper lamina propria, thickening of the basement membrane, and lichenoid mucositis with a deep or perivascular inflammatory infiltrate.[13] The PAS stain was used to reveal the presence of basement membrane thickening.[13] Records without specific information about the diagnosis of SLE, as well as cases with suspected drug-induced oral ulcers, were excluded.

Data sources

Data were collected in August 2022 from information provided by the clinician in the patients' records, as follows: sex, age, skin color, and skin manifestations. The characteristics of the oral lesions were described in terms of anatomical location, clinical aspects, and clinical differential diagnosis. The latter category consisted of immune-mediated diseases, fungal and protozoal diseases, viral and bacterial infections, oral potentially malignant disorders, malignant neoplasms, and others.

Data analysis

Data were tabulated using Microsoft Office Excel 2019 software (Microsoft® software, Redmond, WA, USA). Descriptive and quantitative analysis was performed using GraphPad Prism software, version 8.0 (San Diego, CA, USA).

Results

This series consisted of 53 (75.7%) women and 17 (24.3%) men, with a female-to-male ratio of 3.1:1. The mean age of the entire sample was 38.4 years (range: 11–77 years), 40.8 years for women and 30.9 years for men. The majority of individuals were white (62.1%) (Table 1).

In 45 cases, one (65.2%) oral anatomical site was affected, followed by 17 cases affected at two (24.6%) sites, three (4.4%) at three sites, and four (5.8%) at four sites or more. The hard/soft palate was the most affected site (n = 33/31.1%). Clinically, oral lesions presented mainly as ulcers (26.6%), erosions (26.6%), and/or white lesions (23.4%). The distribution of the clinical aspects of oral lesions according to each affected anatomical location is presented in Table 2. Figure 1 illustrates the variable clinical findings of SLE-related oral lesions.

Oral biopsies, followed by histopathological analysis, were performed in 50 cases based on a wide list of clinical diagnostic hypotheses, including immune-mediated diseases (71.1%) and viral and bacterial infections (10%), among others. The clinical diagnostic hypotheses of SLE (40%) was the most frequently listed (Table 1). Histological sections revealed hyperkeratosis, alternating atrophy, thickening of the spinous cell layer, and lichenoid mucositis accompanied by lymphocytic and plasmocytic subepithelial infiltrations, often surrounding blood vessels. The patchy deposits in the basement membrane area were identified by PAS staining (Figure 2).

Discussion

This series documents information on oral lesions of 70 individuals with SLE in Latin American countries, predominantly young adult women. These cases often exhibited ulcerated lesions primarily affecting the hard/soft palate. These findings are consistent with former studies and underscore the myriad of oral lesions associated with SLE, which can mimic various other oral diseases.[9,11,14] The oral mucosa may serve as a valuable indicator of early signs of disease activity in individuals with SLE.[11] However, there is no consensus regarding the frequency of oral lesions in these individuals, with the literature reporting involvement varying widely from 11% to 97%.[11,15] SLE is known for its clinical heterogeneity and the absence of pathognomonic characteristics, making the diagnosis of associated oral lesions a challenge, even in patients with risk factors.[5,6]

Approximately 50% of cases with oral lesions related to SLE occurred in individuals in the third and fourth decades of life, as also previously reported.[9,11] Women were diagnosed with SLE at later ages than men, a disparity possibly

Table 1. Clinicodemographic data of individuals from Latin America (n = 70) with oral manifestations related to systemic lupus erythematosus disaggregated by country and pooled sample findings.

	Countries					
Variable	Venezuela (n = 39)	Argentina (n = 13)	Brazil (n = 9)	Mexico (n = 5)	Chile (n = 4)	Total (n = 70)
Sex (n, %)						
Male	13 (33.3)	1 (7.7)	1 (11.1)	1 (20.0)	1 (25.0)	17 (24.2)
Female	26 (66.7)	12 (92.3)	8 (88.9)	4 (80.0)	3 (75.0)	53 (75.8)
Female/male ratio	2:1	12:1	8:1	4:1	3:1	3.1:1
Age, mean (SD), range	38.3 (±17.2), 11–74	34.5 (±10.1), 20–64	34.6 (±21.3), 13–77	52.6 (±5.2), 47–62	41.0 (±13.1), 27–62	38.4 (±16.5), 11–77
Skin color (n, %)						
White	19 (48.8)	7 (53.8)	4 (44.5)	5 (100.0)	1 (25.0)	36 (51.4)
Non-white	10 (25.6)	6 (46.2)	3 (33.3)	–	3 (75.0)	22 (31.4)
NI	10 (25.6)	–	2 (22.2)	–	–	12 (17.2)
Site of involvement (n, %)[a]						
Hard/soft palate	15 (34.8)	10 (37.1)	6 (37.5)	–	2 (22.2)	33 (31.7)
Lips/labial mucosa	13 (30.2)	7 (25.9)	2 (12.5)	–	1 (11.1)	23 (22.1)
Buccal mucosa	8 (18.6)	4 (14.8)	2 (12.5)	3 (33.4)	3 (33.4)	20 (19.2)
Gingiva/alveolar ridge	2 (4.7)	3 (11.1)	3 (18.8)	1 (11.1)	2 (22.2)	11 (10.6)
Tongue	2 (4.7)	3 (11.1)	2 (12.5)	2 (22.2)	1 (11.1)	10 (9.6)
Vestibule	2 (4.7)	–	–	1 (11.1)	–	3 (2.9)
Oropharynx	–	–	–	2 (22.2)	–	2 (1.9)
Retromolar trigone	–	–	1 (6.2)	–	–	1 (1.0)
NI	1 (2.3)	–	–	–	–	1 (1.0)
Clinical aspects of oral lesion (n, %)[a]						
Ulcer	17 (29.8)	6 (23.1)	5 (26.3)	4 (25.0)	2 (18.2)	34 (26.4)
Erosion	13 (22.8)	12 (46.1)	2 (10.5)	4 (25.0)	3 (27.3)	34 (26.4)
White lesion	15 (26.3)	5 (19.2)	4 (21.1)	3 (18.8)	3 (27.3)	30 (23.4)
Erythema	9 (15.7)	2 (7.7)	7 (36.8)	5 (31.2)	2 (18.2)	25 (19.4)
Bulla	–	–	–	–	1 (9.0)	1 (0.7)
Macula	1 (1.8)	1 (3.9)	–	–	–	2 (1.6)
Crust	–	–	1 (5.3)	–	–	1 (0.7)
Desquamative gingivitis	1 (1.8)	–	–	–	–	1 (0.7)
NI	1 (1.8)	–	–	–	–	1 (0.7)
Diagnostic clinical hypotheses (n, %)[a]						
Immune-mediated diseases	33 (84.7)	8 (32.0)	13 (76.4)	5 (100.0)	5 (71.4)	64 (68.8)
Fungal and protozoal diseases	–	1 (4.0)	1 (5.9)	–	–	2 (2.1)
Viral and bacterial infections	–	8 (32.0)	1 (5.9)	–	–	9 (9.7)
Oral potentially malignant disorders	2 (5.1)	1 (4.0)	–	–	2 (28.6)	5 (5.4)
Malignant neoplasms	–	–	1 (5.9)	–	–	1 (1.1)

(continued)

Table 1. (continued)

Variable	Countries					
	Venezuela (*n* = 39)	Argentina (*n* = 13)	Brazil (*n* = 9)	Mexico (*n* = 5)	Chile (*n* = 4)	Total (*n* = 70)
Others	2 (5.1)	7 (28.0)	–	–	–	9 (9.7)
NI	2 (5.1)	–	1 (5.9)	–	–	3 (3.2)
Skin manifestations (*n*, %)						
No	–	5 (38.5)	4 (44.5)	–	2 (50.0)	11 (15.7)
Yes	30 (76.9)	8 (61.5)	5 (55.5)	–	2 (50.0)	45 (64.3)
NI	9 (23.1)	–	–	5 (100.0)	–	14 (20.0)
Oral biopsy (*n*, %)						
No	–	6 (46.2)	7 (77.8)	5 (100.0)	2 (50.0)	20 (28.6)
Yes	39 (100.0)	7 (53.8)	2 (22.2)	–	2 (50.0)	50 (71.4)

Note: NI, not informed; SD, standard deviation.

[a]For site of involvement, clinical aspects of oral lesions and diagnostic clinical hypotheses, the unit of analysis was not the number of individuals, since each individual evaluated could have been affected at more than one anatomical site with multiple clinical manifestations, and the clinician could have formulated more than one diagnostic hypothesis.

Table 2. Distribution of clinical aspects in terms of site of involvement of individuals with oral manifestations related to systemic lupus erythematosus.

	Site of involvement* (*n*, %)							
Variable	Hard/soft palate	Lips/labial mucosa	Buccal mucosa	Gingiva/ alveolar ridge	Tongue	Vestibule	Oropharynx	Retromolar trigone
Clinical aspects								
Ulcer	22 (35.5)	11 (25.0)	9 (20.9)	6 (26.0)	8 (34.8)	1 (20.0)	2 (33.4)	1 (50.0)
Erosion	19 (30.6)	17 (38.6)	9 (20.9)	5 (21.7)	5 (21.7)	–	2 (33.3)	–
White lesion	9 (14.5)	7 (15.9)	16 (37.3)	5 (21.7)	6 (26.1)	3 (60.0)	–	–
Erythema	10 (16.2)	6 (13.6)	7 (16.3)	4 (17.4)	3 (13.0)	1 (20.0)	2 (33.3)	1 (50.0)
Macula	1 (1.6)	2 (4.6)	1 (2.3)	1 (4.4)	1 (4.4)	–	–	–
Bulla	–	–	1 (2.3)	–	–	–	–	–
Crust	1 (1.6)	1 (2.3)	–	1 (4.4)	–	–	–	–
Desquamative gingivitis	–	–	–	1 (4.4)	–	–	–	–

Note: *For the site of involvement and clinical aspects of oral lesions, the unit of analysis was not the number of individuals, since each individual evaluated could have been affected at more than one anatomical site with multiple clinical manifestations.

influenced by hormonal and genetic factors.[16] Interestingly, the average age of patients with SLE in Chile and Mexico was higher than in other countries and was similar to the average age of an Irish cohort of patients with severe lupus, many of whom had a well-established SLE.[14] In this line, expert opinions support the notion that the diagnosis of oral ulcers regarding early and established SLE is similar (45% *vs*. 46%).[17] This certainly occurs because studies do not separate the clinical aspects of oral lesions, in addition to the fact that lichenoid lesions are of no clinical significance in worsening or reactivating the disease, whereas ulcers may have such an action. It should also be hypothesized that those who perform assessments of the oral mucosa are often not experts in oral diagnosis.[18]

Oral lesions of SLE are described as areas of well-defined redness (erythema) or erosion with central white papules surrounded by white radiating striae.[5,6,11] Herein, ulcers and erosions, followed by white lesions, were the predominant findings among patients with oral SLE. These lesions can be painful and cause discomfort in affected individuals, with a far-reaching negative impact on their oral health-related quality of life.[19] Similar to the findings of the present study, the literature shows that the hard and soft palate is frequently affected.[5,6,11] This involvement can be helpful in differentiating SLE from conditions such as oral lichen planus, which may have a different distribution. Other locations also include the buccal mucosa, lips, and gingiva.[6]

Oral lichenoid drug reactions, oral lichenoid contact hypersensitivity reaction, oral leukoplakia, mucous membrane pemphigoid, pemphigus vulgaris, chronic graft-versus-host disease, chronic ulcerative stomatitis, and viral infections, such as herpes simplex virus are among the differential diagnoses of oral lesions in SLE.[5,6] However, distinguishing between these conditions and SLE-related oral lesions can pose challenges due to overlapping clinical features.[6] Of clinical relevance, the absence of Nikolsky's sign, typically used to differentiate intraepidermal blisters from subepidermal blisters in pemphigus vulgaris, is not a characteristic feature in oral SLE.[20] Clinicians should be vigilant in recognizing subtle differences and consider referral to a specialist when uncertainty arises.[21] Referral indications may include atypical or refractory lesions, lesions with unusual presentation or distribution, or the presence of systemic symptoms.[18] Hence, a multidisciplinary approach involving rheumatologists, dermatologists, oral medicine specialists, and oral pathologists is crucial to enhance diagnostic accuracy and optimize patient care.[21]

Performing an oral biopsy can be helpful in confirming the diagnosis and guiding appropriate management of oral SLE.[13,17] Histopathologically, oral SLE comprises an interface mucositis along with a lymphocytic infiltrate, apoptotic keratinocytes, and hydropic degeneration of the basal layer. These features are consistent with the mucosal counterpart of interface dermatitis seen in cutaneous lupus lesions.[5,13] In this study, our primary focus was not to relate histopathological findings to the course of the disease or to correlate them with clinical characteristics of oral lesions. However, the differentiation between SLE-related oral lesions and other diseases such as oral lichen planus, can be challenging, since both conditions can exhibit similar histopathological findings such as interface mucositis. In cases of oral lichen planus, the interface change exhibits a lichenoid pattern with a higher number of apoptotic keratinocytes, while in cases of SLE the underlying intense perivascular inflammatory infiltrate is typical. In oral SLE, the epithelium may exhibit

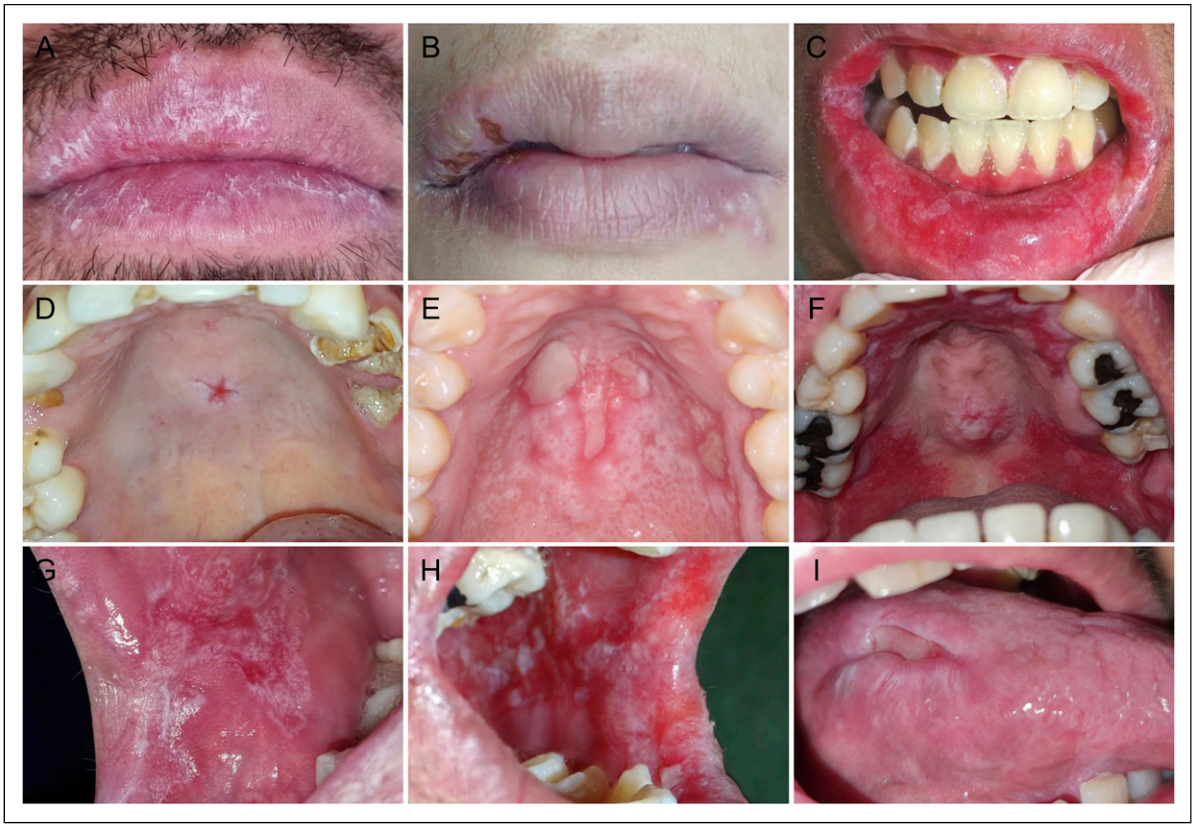

Figure 1. Oral lesions of systemic lupus erythematosus. (A) Diffuse brownish-white plaques with a desquamation appearance on the lips. (B) Multiple erythematous and ulcerated lesions on the upper lip, as well as whitish vesicles located at the transition between the semi-mucosa of the lower lip and the skin. (C) Diffuse ulcerative lesions and irregular white plaques in the upper and lower labial mucosa and commissure. Note that poor oral hygiene is due to painful lesions. (D) Single erythematous ulcerated lesion with whitish borders resembling a "star" format in the hard palate. (E) Multiple yellowish-white vesicles/bullae surrounded by an erythematous halo in the hard palate. (F) Radiating keratotic striae surrounded by erythematous zones of the soft palate. Note reddish-white erosions in the midline of the hard palate. (G) Ulcerations and erosions in the right buccal mucosa contiguous to the labial commissure, exhibiting fine white striae radiating around its periphery. (H) Radiant keratotic striae surround the erythematous and erosive zones of the left buccal mucosa, extending to the labial mucosa and commissure. (I) Single ulcerated lesion of yellowish-white color with base infiltration and hardened high margins on the right lateral border of the tongue. Note the fine radiating white striae at the periphery surrounding the lesion.

atrophy or pseudoepitheliomatous hyperplasia and hyperkeratosis with keratin plugging, whereas in oral lichen planus, the epithelium is generally atrophic and the thickness of the ret ridges is reduced and may exhibit hyperplasia.[5,22] These two conditions can also generally be distinguished by the presence of patchy deposits of PAS-positive material in the basement membrane area and subepithelial edema in oral SLE.[5,13] Besides, the presence of linear or granular deposition of immunoglobulins (i.e., IgM and IgG) and complement C3 in the basement membrane zone is a hallmark of autoimmune diseases, including SLE.[23] In cases of oral lichen planus, on the other hand, the presence of fibrinogen along the basement membrane zone is a distinguishing feature that may be observed by direct immunofluorescence.[23] Unfortunately, additional tests such as this last cited approach were unavailable in the services investigated, a shortcoming of our series.

The contribution to the literature on the clinicopathological aspects of SLE-related oral lesions demonstrates the strength of this Latin American collaborative study. However, socioeconomic and cultural factors, in addition to the fact that oral examination is often overlooked in individuals with SLE, may contribute to the underdiagnosis of oral lesions.[5,14] In certain regions of Latin America, oral health may not be given as much attention or priority as other health issues, leading to delays in diagnosis and treatment of oral lesions of SLE.[18] This aligns with recent global epidemiological data revealing that SLE has a higher occurrence in high-income countries.[4]

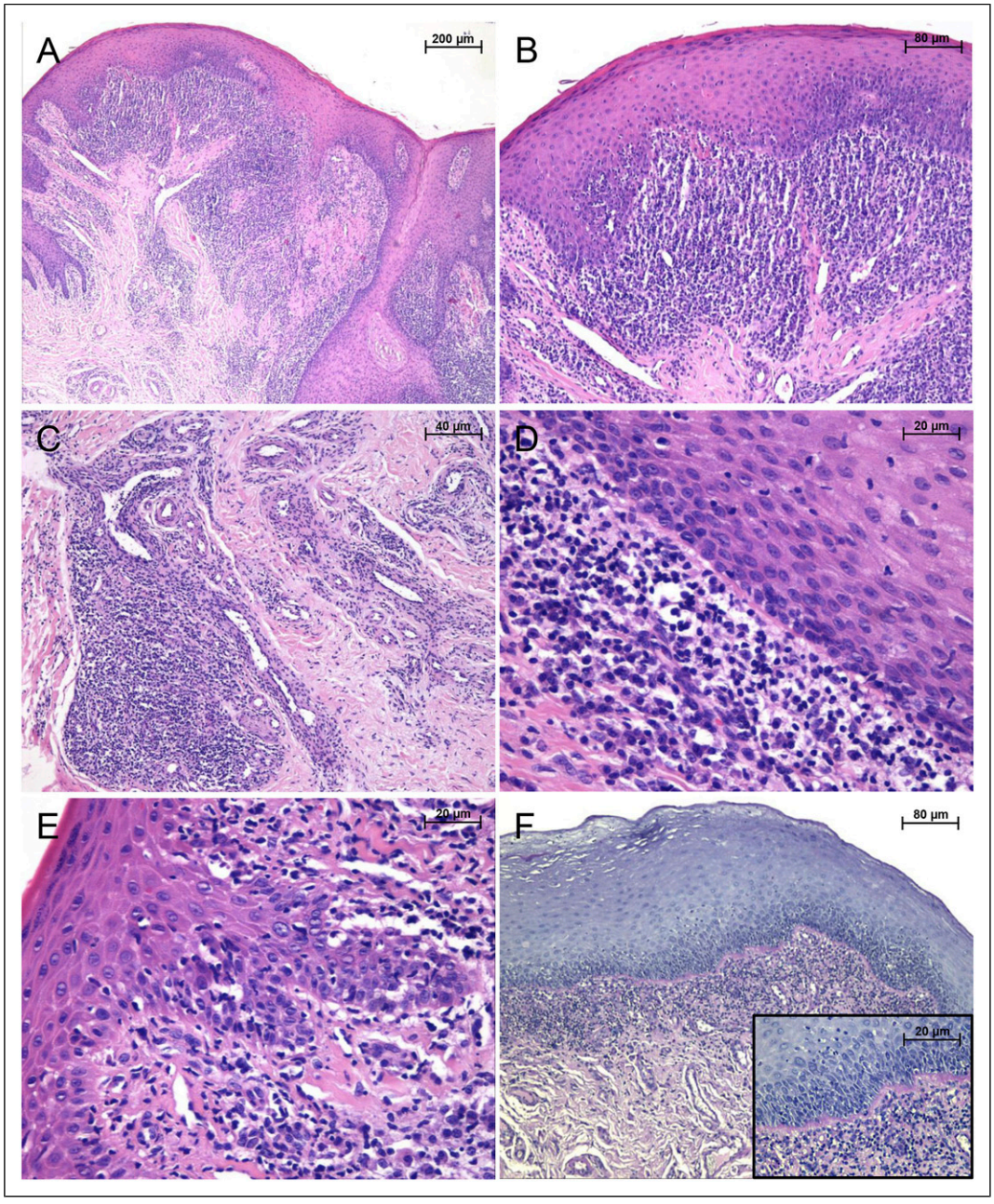

Figure 2. Histopathological features of oral lupus erythematosus. (A) Low power view of the lesion revealing hyperkeratosis of irregular thickness with degeneration of the basal cell layer, and (B) abundant lymphocytic inflammatory infiltrate in the connective tissue. High-power photomicrographs showing details of (C) blood vessels with basement membrane thickening and a perivascular infiltrate, (D) epithelial basement membrane thickening, and (E) interface mucositis. (F) Low- and high-power (inset) views revealing patchy deposits of a periodic acid-Schiff (PAS)-positive material in the basement membrane zone (hematoxylin and eosin staining: 40×, 100×, 200× and 400× magnification; PAS staining: 100× and 400× magnification).

In summary, oral lesions of SLE encompass a wide range of clinical features, with the most frequently observed presentations including ulcers, erosions, and white lesions. These lesions often affect young female individuals. When clinicians encounter unusual oral lesions in patients without an apparent local cause, it is essential to consider the possibility of an underlying systemic condition such as SLE. An early recognition of these signs within a multidisciplinary approach can lead to a timely diagnosis with appropriate treatment and monitoring of the progression of oral lesions along the systemic therapy, which is necessary to build data that will support the patients' overall health and well-being.

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Author contributions

J.A.A.A., C.H.F., J.L.C.C., J.V.L.V., V.A.M., F.S.L., and J.R.T., organized the data of the clinical cases. M.V.D., I.M.A., J.M.P.S., G.G., E.P., R.P., J.C.R.P., S.A.R., F.J.T.N., M.S.I., C.F.W.N., P.M.A., R.M.F., K.C.T., R.A.O., J.G., R.T., S.S.S.N., D.A.C.A., E.F.M., V.M.P., M.G.O., F.V., and K.L.O. contributed cases from their services and reviewed all cases. B.A.B.A., V.Z.D., I.L.C., and T.A.S. contributed to the design of the study, while L.G.A. was responsible for data interpretation. J.A.A.A. took the lead in writing the manuscript. F.P.F., R.A.M., and J.C.C.X.J., assisted in project supervision and contributed to the interpretation of the results. B.A.B.A. and J.R.T. contributed to the conception of the study. All authors reviewed the manuscript.

Declaration of conflicting interests

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