SHORT COMMUNICATION

Oral Manifestations of Bullous Systemic Lupus Erythematosus: A Systematic Review

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Bullous systemic lupus erythematosus (BSLE) is a rare, acquired, subepidermal autoimmune blistering disease occurring in the setting of systemic lupus erythematosus (SLE). It presents as a widespread vesiculobullous eruption with neutrophilic infiltrates on histology and an immunologic profile classically characterized by autoantibodies to type VII collagen (1). The oral mucosa may be involved in up to 50% of cases, but this feature has not been well described (2–4). We thus sought to further characterize the epidemiological, clinical, and morphological features of oral involvement in BSLE.

MATERIALS AND METHODS

Following registration on the International Prospective Register of Systematic Reviews (PROSPERO, CRD42024611504), a systematic search of Web of Science, PubMed, and EMBASE was conducted from inception to 21 August 2024 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Search terms used were (bullous systemic lupus erythematosus) OR (BSLE) OR (bullous SLE) OR (bullous lupus). Article screening, duplicate identification, and independent full-text review were performed using the web platform Rayyan (5). A total of 59 articles comprising 77 BSLE patients was identified with inclusion and exclusion criteria as indicated (Fig. S1; Table SI).

RESULTS

Oral involvement was documented in 68.8% (53/77) of patients with BSLE. BSLE patients with oral involvement (oBSLE) were significantly younger than those without oral involvement (non-oBSLE; 33.8 ± 15.0 vs 44.6 ± 18.4 years, $p = 0.017$), and a higher proportion of oBSLE patients were female (94.3% [50/53] vs 79.2% [19/24], $p = 0.043$; **Table I**). Of the 23 oBSLE patients for whom race and ethnicity was reported, 69.6% were Black, 26.1% were Asian Pacific Islander, 4.3% were Hispanic/Latino, and none were White (**Table II**).

Amongst the 53 patients with oBSLE, the lips were the most common site of involvement (67.9% [36/53]; see Table II). On review of available photographs, the morphology of labial oBSLE was clinically distinctive, manifesting as tense, linearly arranged vesicles along the vermilion without erythema, erosions, or haemorrhagic crusting (**Fig. 1**). Isolated lip involvement was observed in 22.6% (12/53), and simultaneous lip and intra-oral involvement was observed in 24.5% (13/53; data not shown). The vermilion lip was affected more than twice as often as the mucosal lip (52.8% [19/36] vs 22.2% [8/36], respectively).

Table I. Clinical and demographic characteristics of bullous systemic lupus erythematosus (BSLE) patients with and without oral involvement

Characteristic	Oral BSLE *n* (%)	Non-oral BSLE *n* (%)	*p*-value
Demographic features			
Age, mean ± SD, years	33.8 ± 15.0	44.6 ± 18.4	**0.017**
Sex			
Female	50/53 (94.3%)	19/24 (79.2%)	**0.043**
Male	3/53 (5.7%)	5/24 (20.8%)	
Race/ethnicity (if reported)			NS
Black	16/23 (69.6%)	3/5 (60%)	
White	0/23 (0%)	1/5 (20%)	
Hispanic/Latino	1/23 (4.3%)	0/5 (0%)	
Asian or Pacific Islander	6/23 (26.1%)	1/5 (20%)	
Other	0/23 (0%)	0/5 (0%)	
Facial Involvement			**0.002**
Yes	40/53 (75.5%)	7/19 (36.8%)	
No	13/53 (24.5%)	12/19 (63.2%)	

NS: not significant. Bold values indicatge significance.

Intra-oral involvement was documented in 58.5% (31/53) of oBSLE patients, with findings on the buccal mucosa in 28.3% (15/53), palate in 17.0% (9/53), and tongue in 13.2% (7/53). Gingival and oesophageal oBSLE were rare, and isolated palatal involvement was not observed. Interestingly, concurrent facial involvement was observed more than twice as often in oBSLE compared with non-oBSLE patients (75.5% [40/53] vs 36.8% [7/19], $p = 0.002$; see Table I). Of note, isolated oBSLE without cutaneous findings was not seen.

Haematologic abnormalities ranging from minor cytopenias to autoimmune haemolytic anaemia were the most common extracutaneous manifestation, affecting 52.8% (28/53) of oBSLE patients. Lupus nephritis was seen in 18.9% (10/53). Corticosteroids and dapsone were the most common treatments; however, many patients required additional lines of therapy (see Table II).

DISCUSSION

Nearly 70% of our cohort of BSLE patients exhibited oral mucosal involvement, with the vermilion lip and buccal mucosa being the most commonly affected sites. Involvement of the gingiva and tongue occurred rarely. Demographically, most oBSLE patients were Black, a finding that has been anecdotally noted but not previously validated (6). Although BSLE classically exhibits a striking therapeutic response to dapsone, with efficacy rates estimated at >90%, clinical improvement with single-agent dapsone occurred in only approximately 60% of patients in our cohort (4).

Table II. Demographic, clinical, histopathologic, and immunologic features of bullous systemic lupus erythematosus patients with oral involvement

Characteristic	*n* (%)
Demographic features	
Age, mean ± SD, years	33.8 (15)
Sex	
Female	50/53 (94.3%)
Male	3/53 (5.7%)
Race/ethnicity	
Black	16/23 (69.6%)
White	0/23 (0%)
Hispanic/Latino	1/23 (4.3%)
Asian or Pacific Islander	6/23 (26.1%)
Other	0/23 (0%)
Clinical morphology	
Oral involvement	53/53 (100%)
Morphology	
Tense bullae or vesicles	35/53 (66.0%)
Erosions	3/53 (5.7%)
Both	15/53 (28.3%)
Location	
Lips	36/53 (67.9%)
Vermilion	19/36 (52.8%)
Mucosal	8/36 (22.2%)
Unclear	9/36 (25%)
Intra-oral mucosa	31/53 (58.5%)
Buccal mucosa	15/53 (28.3%)
Palate	9/53 (17.0%)
Tongue	7/53 (13.2%)
Gingiva	1/53 (1.9%)
Esophagus	1/53 (1.9%)
Facial involvement	40/53 (75.5%)
Systemic manifestations	
Lupus nephritis	10/53 (18.9%)
Neuropsychiatric or cerebral lupus	2/53 (3.8%)
Haematologic involvement, cytopenias	28/53 (52.8%)
Histopathology	
Subepidermal bullae with neutrophils	44/53 (83.0%)
Dermatitis herpetiformis pattern[a]	15/53 (28.3%)
Subepidermal bullae with sparse inflammation	4/53 (7.5%)
Vacuolar interface +/- apoptotic keratinocytes	4/53 (7.5%)
Mucin deposition	7/53 (13.2%)
Other	4/53 (7.5%)
Direct immunofluorescence	
Staining pattern	
Linear	18/53 (34.0%)
Granular	6/53 (11.3%)
Both	11/53 (20.8%)
Not reported	18/53 (34.0%)
Immunoglobulins present	
IgG	49/53 (92.5%)
IgA	35/53 (66.0%)
IgM	35/53 (66.0%)
IgE	1/53 (1.9%)
C3	36/53 (68.0%)
Indirect immunofluorescence	
Roof	0/28 (0%)
Floor	10/28 (35.7%)
Negative	13/28 (46.4%)
Unspecified	5/28 (17.9%)
Serologic analysis (positive anti-COL7 antibodies)[b]	7/7 (100%)
Treatments	
Glucocorticoids	39/53 (73.6%)
Dapsone	33/53 (62.3%)
Response as single agent	20/33 (60.6%)
Response when combined with other treatments	8/33 (24.2%)
No response	5/33 (15.2%)
Hydroxychloroquine or chloroquine	15/53 (28.3%)
Other conventional immunosuppressants	21/53 (39.6%)
Rituximab	4/53 (7.5%)
IVIg	2/53 (3.8%)
Other	3/53 (5.7%)
Not discussed	6/53 (11.3%)

[a]Dermatitis herpetiformis pattern: neutrophils aggregating within dermal papillae. [b]Only 7 patients had testing for anti-COL7 antibodies.
SD: standard deviation; COL7: type VII collagen; IVIg: intravenous immunoglobulin.

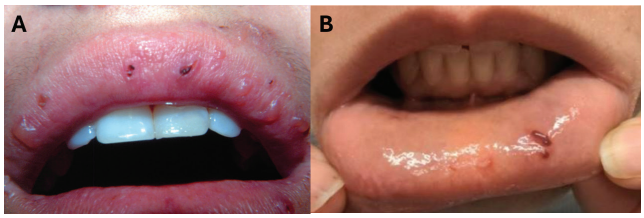

Fig. 1. Distinctive clinical presentation of labial oral bullous lupus erythematosus. (A) Multiple intact tense vesicles along the lip vermilion. (B) Semi-arcuate tense vesicles of lower mucosal lip. (A) reproduced with permission from Nico & Lourenço (2).

Notably, our findings substantiate a prior report emphasizing the phenotypically distinctive features of labial involvement in oBSLE (2). Unlike other lupus-associated oral manifestations, oBSLE presents uniquely as discrete tense vesicles along the lip vermilion with minimal erosion, exudates, or haemorrhagic crusting. Morphologically, these findings also permit distinction of oBSLE from other immunobullous or parainfectious mucosal disorders, including those that may present with desquamative gingivitis, erosive lingual or palatal ulcers, haemorrhagic mucositis, or diffuse intraoral mucosal sloughing.

Limitations of our study include the heterogeneity in descriptions of clinical morphology, the possibility of missing or incomplete data, and the retrospective nature of the analysis. However, our relatively stringent inclusion and exclusion criteria reduces the potential for confounding by other SLE-associated bullous conditions.

Overall, our study presents the first detailed characterization of oral mucosal involvement in BSLE. We advocate that intact vesiculobullae on the vermilion lip be considered a distinguishing feature of this condition.

The authors have no conflicts of interest to declare.

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