APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Bullous systemic lupus erythematosus in a Southeast Asian cohort: High systemic association driving systemic therapy

Chuda Rujitharanawong, Kanokvalai Kulthanan, Papapit Tuchinda, Sasipha Nuttawong, Mananchaya Julraksa, Leena Chularojanamontri

Abstract

Background: Bullous systemic lupus erythematosus (BSLE) is a rare autoimmune blistering disorder occurring in association with systemic lupus erythematosus (SLE). Owing to its rarity, current knowledge remains limited, particularly in Southeast Asian populations.

Objective: This study retrospectively evaluated the clinical, histopathologic, immunofluorescence, and serologic features of BSLE, together with a review of the existing literature.

Method: This review included patients diagnosed with BSLE at Siriraj Hospital, Mahidol University, between 2003 and 2024.

Results: Among 9,055 patients with cutaneous lupus erythematosus, 12 were identified as having BSLE (incidence 0.13%). The median age was 39.5 years with equal sex distribution. Most patients (75%) presented with BSLE at the time of SLE diagnosis, while others developed it later. Lesions appeared on sun-exposed and non-sun-exposed areas, mainly the extremities, and mucosal involvement occurred in 33.3%. Direct immunofluorescence most frequently demonstrated immunoglobulin (Ig) G deposition (91.7%), followed by complement 3 (83.3%), IgM (75%), and IgA (50%), typically with linear and/or granular deposition of IgG and C3 along the basement membrane zone. Antinuclear antibodies were present in all patients. Systemic involvement was common (75%), most frequently affecting the kidneys (66.7%), followed by hematologic abnormalities (58.3%). Owing to disease severity, most patients required treatment with systemic corticosteroids in combination with immunosuppressive agents rather than dapsone alone to achieve disease control.

Conclusions: This study and literature review highlight that, although BSLE is an uncommon cutaneous manifestation of SLE, it is strongly associated with systemic involvement, particularly renal and hematologic disease, which often necessitates treatment with immunosuppressive agents.

Key words: bullous systemic lupus erythematosus, cutaneous lupus erythematosus, autoimmune blistering disease, direct immunofluorescence, pathogenesis

Citation:
Rujitharanawong, C., Kulthanan, K., Tuchinda, P., Nuttawong, S., Julraksa, M., Chularojanamontri, L. (0000). Bullous systemic lupus erythematosus in a Southeast Asian cohort: High systemic association driving systemic therapy. *Asian Pac J Allergy Immunol*, 00(0), 000-000. https://doi.org/10.12932/ap-241125-2180

Affiliation:
Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Corresponding author:
Leena Chularojanamontri
2 Wanglang Road, Siriraj, Bangkok Noi, Bangkok 10700, Thailand
E-mail: leenajim@gmail.com

Introduction

Systemic lupus erythematosus (SLE) has an annual incidence of approximately 1-10 per 100,000 population and a prevalence ranging from 5.5 to 130 per 100,000.[1] Cutaneous lupus erythematosus (CLE), a common manifestation of SLE, has an incidence of 3-4 per 100,000 and a prevalence of approximately 70 per 100,000 in population-based studies from the United States and Europe.[1-7] Vesiculobullous manifestations in SLE are rare, affecting less than 5% of patients.[8] Blistering disorders associated with SLE can be broadly classified into three main categories.[8] The first includes lupus erythematosus-specific vesiculobullous lesions, which occur secondary to severe interface dermatitis in active CLE and are histologically marked by vacuolar alteration at the basement membrane zone (BMZ) and mononuclear cell infiltrates in the upper dermis. The second category comprises coincidental autoimmune blistering diseases that may coexist with SLE, such as dermatitis herpetiformis,[9-11] bullous pemphigoid,[12-14] and pemphigus erythematosus.[15] The third category is bullous systemic lupus erythematosus (BSLE), a distinct subepidermal blistering disorder characterized by autoantibody-mediated damage at the BMZ.[16-18]

BSLE is clinically presented with acute-onset of vesiculobullous eruptions. Reported incidences of BSLE include 0.2% in Thailand and Sudan, 2.1% in France, and 3% in Singapore.[16,17,19,20] In pediatric populations, BSLE remains rare, with a prevalence of 1% reported in a Brazilian cohort.[21] BSLE predominantly affects women in early to middle adulthood, most frequently between the second and fourth decades of life.[22] Approximately 40-50% of patients develop bullous eruptions at the onset of SLE, whereas the remaining 50-60% experience blister formation after their initial SLE diagnosis. The interval between SLE onset and the appearance of bullae ranges from 2.5 to 40 months.[16,23] The diagnostic criteria for BSLE were first described in 1983 and later revised in 1988 to include the following criteria; (i) meeting the diagnosis of SLE; (ii) vesiculobullous eruptions; (iii) histopathology showing a subepidermal blister with a predominantly neutrophilic infiltrate; (iv) direct immunofluorescence (DIF) with predominate IgG and/or IgM, at the BMZ; (v) indirect immunofluorescence (IIF) showing either negative or positive binding of autoantibodies to the BMZ using the salt-split skin technique. Due to its rarity and clinical resemblance to other autoimmune blistering disorders, BSLE often remains underrecognized. Enhanced awareness and improved recognition are essential for the accurate diagnosis and management of BSLE. Therefore, this study aimed to retrospectively review the clinical manifestations, histopathologic features, immunofluorescence findings, and serologic profiles of BSLE, along with a review of previously published literature.

Material and methods

This retrospective review included patients diagnosed with BSLE at Siriraj Hospital, Mahidol University, between 2003 and 2024. Electronic medical records were searched using the ICD-10 codes L93, L13.9, and M32 to identify patients with CLE and BSLE. The diagnosis of BSLE was established using histopathology, direct immunofluorescence, direct salt-split skin testing, and relevant SLE serology, as anti-type VII collagen ELISA is not routinely available at our center. Data on demographics, clinical manifestations, relevant investigations, and treatment outcomes were collected. Cutaneous disease was considered controlled when no active skin lesions were present for at least 2 months, and partially controlled when lesions improved but did not fully resolve. Systemic involvement was considered controlled when all abnormalities normalized for at least 2 months, partially controlled when abnormalities improved without normalizing, and uncontrolled when no improvement was seen. This study was approved by the Siriraj Institutional Review Board. All analyses were performed using SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as a *P*-value less than 0.05.

Results

Among 9,055 patients diagnosed with CLE and/or SLE between January 2003 and December 2024, 12 were diagnosed with BSLE, yielding an incidence of 0.13% in this cohort. The median age at BSLE onset was 39.5 years (range: 23-65), with an equal distribution between males and females. **Table 1** summarizes the clinical manifestations, histopathologic features, immunofluorescence findings, and treatment outcomes of patients in our cohort. Nine patients (75%) developed BSLE at the onset of SLE, while 2 (16.7%) and 1 (8.3%) patient developed BSLE at 4 months and 24 months after SLE diagnosis, respectively. Cutaneous involvement was limited to sun-exposed areas in 7 patients (58.3%), restricted to sun-protected sites in 1 patient (8.3%), and affected both regions in 4 patients (33.3%). The upper extremities were the most frequently involved anatomical site, affected in 8 patients (66.7%), followed by the lower extremities in 6 patients (50%). Mucosal involvement was identified in 4 patients (33.3%), all of whom exhibited lesions confined to the oral mucosa. Antinuclear antibodies (ANA) were detected in all patients, while anti-dsDNA were present in 4 patients (33.3%). Systemic involvement was documented in 9 patients (75%), reflecting a high prevalence of multisystem diseases. Renal involvement was noted in 8 patients (66.7%), most commonly presenting as proteinuria in 6 patients. Hematologic abnormalities were identified in 7 patients (58.3%), with anemia being the most frequent manifestation (6 patients).

Table 1. Clinical, investigating, and therapeutic characteristics of patients with bullous systemic lupus erythematosus.

Case	Sex/Age	Onset	Distribution	Histopathology and Immunofluorescence	Systemic involvement	Treatment	Outcome*	Recurrence/ Duration
1.	M/27	at onset	***Sun-exposed:*** neck, arm, knee ***Sun-protected:*** back ***Mucosa:*** yes (oral)	***Left calf:*** ***Histo:*** subepidermal blister with mixed neutrophils and eosinophil ***Direct immunofluorescence:*** ***IgG*** linear DEJ (1+) ***IgA*** negative ***IgM*** focal granular DEJ (1+), SBV (1+/mod) ***C3*** linear/granular DEJ (1+), SBV (1+/mod)	***Hematology*** - anemia (DCT +) ***Renal*** - hematuria	***Response*** - prednisolone (30 mg/d) - methotrexate (15 mg/wk) - chloroquine (250 mg/d) ***Previous non-response*** - cyclophosphamide (100 mg/d) - azathioprine (100 mg/d)	***Skin*** control ***Systemic*** control	ACLE/ 9 y
2.	M/49	at onset	***Sun-exposed:*** extremities ***Sun-protected:*** trunk ***Mucosa:*** no	***Right forearm*** ***Histo:*** subepidermal blister with predominant neutrophils and scattered eosinophils ***Direct immunofluorescence*** ***IgG*** linear DEJ (1+), ENS (1+) ***IgA*** linear/granular DEJ (1+) ***IgM*** granular DEJ (1+) ***C3*** linear DEJ (1+)	***Hematology*** - anemia (DCT +) - leukopenia ***Renal*** - rising creatinine	***Response*** - prednisolone (30 mg/d) - chloroquine (250 mg/d) - azathioprine (75 mg/d)	***Skin*** control ***Systemic*** control	No/ 6 y
3.	F/33	after 24 m	***Sun-exposed:*** face ***Mucosa:*** no	***Face*** ***Histo:*** subepidermal blister with neutrophil predominate and focal vasculitis ***Direct immunofluorescence:*** ***IgG*** granular DEJ (2+), appendage (2+/few) ***IgA*** granular DEJ (1+) ***IgM*** granular DEJ (1+) ***C3*** granular DEJ (1+), appendage (1+/few)	***Hematology*** - anemia - leukopenia ***Renal*** - rising creatinine - proteinuria - hematuria	***Response*** - prednisolone (40 mg/d) - chloroquine (250 mg/wk) - azathioprine (150 mg/d) - mycophenolate mofetil (2 g/d)	***Skin*** control ***Systemic*** partial control	No/2 y
4.	F/54	at onset	***Sun-exposed:*** arm, hand ***Mucosa:*** no	***Right hand*** ***Histo:*** subepidermal vesicle with mixed infiltration of neutrophils and eosinophils ***Direct immunofluorescence:*** ***IgG*** negative ***IgA*** focal granular DEJ (1+) ***IgM*** focal granular DEJ (1+), colloid bodies (1+/few) ***C3*** negative	**No**	***Response*** - dapsone (200 mg/d)	***Skin*** control	No/ 7 y

Asian Pac J Allergy Immunol DOI 10.12932/AP-241125-2180

Table 1. (Continued)

Case	Sex/Age	Onset	Distribution	Histopathology and Immunofluorescence	Systemic involvement	Treatment	Outcome*	Recurrence/ Duration
5.	F/28	after 4 m	***Sun-exposed:*** neck, chest wall ***Mucosa:*** yes (oral)	***Left postauricular area*** ***Histo:*** subepidermal blister with neutrophil predominate ***Direct immunofluorescence:*** ***IgG*** linear DEJ (2+) ***IgA*** linear DEJ (1+) ***IgM*** granular DEJ (1+) ***C3*** negative	***Hematology*** - anemia (DCT -) ***Renal*** - rising creatinine - proteinuria - hematuria	***Response*** - prednisolone (30 mg/d) - hydroxychloroquine (200 mg/d) - dapsone (100 mg/d) - mycophenolate mofetil (1 g/d) - Intravenous cyclophosphamide (500 mg*6 dose)	***Skin*** control ***Systemic*** uncontrol	ACLE/ 3 y
6.	F/24	after 4 m	***Sun-exposed:*** face, neck, ear, hand ***Mucosa:*** no	***Right thigh*** ***Histo:*** subepidermal blister with predominate neutrophils and eosinophils ***Direct immunofluorescence:*** ***IgG*** ENS (1+) ***IgA*** negative ***IgM*** colloid bodies (2+ few) ***C3*** linear BMZ (2+) ***Direct salt-spilt study:*** ***C3*** staining at floor	***Hematology*** - anemia (DCT +) ***Renal*** - proteinuria - hematuria	***Response*** - prednisolone (30 mg/d) - chloroquine (250 mg/d) - dapsone (100 mg/d) - mycophenolate mofetil (1 g/d)	***Skin*** control ***Systemic*** control	No/ 4 y
7.	M/63	at onset	***Sun-protected:*** thigh ***Mucosa:*** yes (oral)	***Left thigh*** ***Histo:*** subepidermal blister with neutrophils and eosinophils ***Direct immunofluorescence:*** ***IgG*** granular BMZ (1+), SBV (2+/mod), appendage (1+/few) ***IgA*** negative ***IgM*** SBV (1+/few), colloid bodies (1+/few) ***C3*** granular DEJ (1+), SBV (1+/mod), appendage (1+/few)	***Hematology*** - leukopenia - thrombocytopenia	***Response*** - prednisolone (20 mg/d) - hydroxychloroquine (200 mg/d) - dapsone (100 mg/d) - colchicine (1.2 mg/d)	***Skin*** partial control ***Systemic*** control	No/ 2 y
8.	M/46	at onset	***Sun-exposed:*** forearm ***Mucosa:*** no	***Left forearm*** ***Histo:*** subepidermal blister with neutrophil predominate ***Direct immunofluorescence:*** ***IgG*** linear BMZ (2+), appendage (2+/few) ***IgA*** negative ***IgM*** negative ***C3*** linear BMZ (1+) ***Direct salt-split study:*** ***IgG*** staining at floor ***C3*** staining at floor	**No**	***Response*** - prednisolone (20 mg/d)	***Skin*** control	No/ 10 y

Table 1. (Continued)

Case	Sex/Age	Onset	Distribution	Histopathology and Immunofluorescence	Systemic involvement	Treatment	Outcome*	Recurrence/ Duration
9.	M/65	at onset	***Sun-exposed:*** arm, leg ***Sun-protected:*** trunk ***Mucosa:*** no	***Left arm*** ***Histo:*** subepidermal bullae ***Direct immunofluorescence:*** ***IgG*** linear BMZ (2+) ***IgA*** negative ***IgM*** negative ***C3*** granular BMZ (1+), SBV (2+/mod)	**No**	***Response*** - prednisolone (20 mg/d) - dapsone (100 mg/d)	***Skin*** control	No/ 1 y
10.	F/50	at onset	***Sun-exposed:*** arm ***Sun-protected:*** thigh ***Mucosa:*** no	**Right thigh** **Histo:** subepidermal blister with neutrophils and eosinophils infiltration at BMZ **Direct immunofluorescence:** ***IgG*** linear BMZ (2+) ***IgA*** negative ***IgM*** negative ***C3*** linear BMZ (1+)	***Hematology*** - anemia (DCT N/A) - leukopenia ***Renal*** - proteinuria	***Response*** - prednisolone (60 mg/d) - chloroquine (250 mg/d) - aspirin (81 mg/d) - mycophenolate mofetil (1 g/d) ***Previous non-response*** - cyclophosphamide (50 mg/d)	***Skin*** control ***Systemic*** control	No/ 12 y
11.	F/25	at onset	***Sun-exposed:*** hand, arm, leg ***Mucosa:*** yes (oral)	**Right hand** **Histo:** subepidermal blister with neutrophil predominate **Direct immunofluorescence:** ***IgG*** focal granular BMZ (1+), ENS (1+) ***IgA*** focal granular BMZ (1+) ***IgM*** granular BMZ (3+), appendage (1+/few) ***C3*** granular BMZ (1+)	***Renal*** - rising creatinine - proteinuria	***Response*** - prednisolone (40 mg/d) - chloroquine (500 mg/wk)	***Skin*** control ***Systemic*** uncontrol	No/ 11 y
12.	M/23	at onset	***Sun-exposed:*** hand ***Mucosa:*** no	**Right hand** **Histo:** subepidermal blister with predominate neutrophils admixed with eosinophils **Direct Immunofluorescence** ***IgG*** granular BMZ (1+) ***IgA*** focal granular, BMZ (1+) ***IgM*** focal granular, BMZ (1+) ***C3*** granular BMZ (1+)	***Renal*** - proteinuria	N/A	N/A	N/A

Abbreviation: M, male; F, female; NA, not available; Ig, immunoglobulin; BMZ, basement membrane zone; ENS, epidermal nuclear staining; Histo, histopathology; m, month; wk, week; d, day; mod, moderate; SBV, superficial blood vessels; C, complement; DCT, direct coombs' test;

*Controlled cutaneous lesions were defined as the absence of active skin lesions for ≥ 2 months. Partial control indicated improvement without complete resolution. Controlled systemic involvement referred to normalization of abnormalities for ≥ 2 months, partial control to improvement without normalization, and uncontrolled involvement to no improvement.

Table 2. Direct immunofluorescence patterns in patients with bullous systemic lupus erythematosus.

Patterns	IgG	IgA	IgM	C3
Linear deposit at BMZ	6 (50%)	1 (8.3%)	0 (0%)	4 (33.3%)
Granular deposit at BMZ	4 (33.3%)	4 (33.3%)	7 (58.3%)	5 (41.7%)
Linear and granular deposit at BMZ	0 (0%)	1 (8.3%)	0 (0%)	1 (8.3%)
Epidermal nuclear staining	3 (25%)	0 (0%)	0 (0%)	0 (0%)
Appendage	3 (25%)	0 (0%)	1 (8.3%)	2 (16.7%)
Superficial dermal blood vessels	1 (8.3%)	0 (0%)	2 (16.7%)	2 (16.7%)
Colloid bodies	0 (0%)	1 (8.3%)	3 (25%)	0 (0%)

Abbreviation: BMZ, basement membrane zone; Ig, immunoglobulin; C, complement;

DIF findings are summarized in **Table 2.** IgG was the most frequently detected immunoreactant in 11 patients (91.7%), followed by complement 3 (C3) (10 patients, 83.3%), IgM (9 patients, 75%), and IgA (6 patients, 50%). The predominant pattern was linear and/or granular deposition of IgG and C3 along the BMZ, identified in 11 patients (91.7%). Granular IgM deposition, commonly seen in other subtypes of CLE, was noted in 7 patients (58.3%). Additional findings included immunoreactant deposition in appendage structures in 4 patients (33.3%), superficial dermal blood vessels in 3 patients (25%), and colloid bodies in 3 patients (25%). Epidermal nuclear staining with IgG was also noted in 3 patients (25%).

Treatment Response and Outcomes

Most patients received a combination of corticosteroids and immunosuppressive agents to manage both cutaneous and systemic manifestations (**Table 1**). Prednisolone was prescribed in 10 of 12 patients (83.3%) at a mean dose of 32 mg/day (range 20-60 mg), followed by antimalarial agents in 6 patients (50%) at 250-500 mg/day. Mycophenolate mofetil was the most commonly used immunosuppressive agent. Dapsone monotherapy was used in only one patient without systemic involvement. Cutaneous disease control was achieved in 10 patients (83.3%). During a median follow-up period of 7 years (range: 1-12 years), two patients (16.7%) experienced recurrence of CLE, presenting as acute CLE at 3 and 9 years after BSLE onset.

Discussion

Figure 1 illustrates the proposed pathogenesis of BSLE. Genetic susceptibility combined with environmental triggers, most notably ultraviolet radiation (UVR), play a critical role in the development of CLE lesions, particularly in sun-exposed areas. In CLE, UVR induces prolonged keratinocyte apoptosis, with apoptotic cells persisting for up to 72 hours, compared to the more efficient clearance observed in healthy individuals.[24] Inefficient clearance results in secondary necrosis and the release of intracellular antigens, facilitating the formation of autoantibody-antigen complexes.[25] The accumulation of apoptotic debris further contributes to the generation of autoantibodies, including those directed against type VII collagen. The hallmark of BSLE pathogenesis is primarily mediated by circulating autoantibodies targeting type VII collagen, particularly its noncollagenous domain 1, resulting in disruption of the BMZ junction and formation of subepidermal blisters.[26] In addition to this direct mechanism, immune complex deposition and complement activation promote neutrophil recruitment, a key histopathologic feature of BSLE.[27-29] These immune complexes also activate type I interferon (IFN) pathways.[25] IFN-α induces nitric oxide synthase and mediates oxidative tissue damage.[30,31] The interplay between IFN activation and nitric oxide-driven inflammation contributes to a self-perpetuating proinflammatory loop that may exacerbate tissue injury in both CLE and SLE.[32-34] Reported evidence suggests that BSLE is associated with a higher frequency of systemic involvement, including lupus nephritis and hematologic abnormalities. This observation supports the hypothesis that IFN-mediated pathways may underlie both cutaneous and systemic disease manifestations.[35-37] Nevertheless, the specific cytokines and molecular pathways connecting IFN signaling to the diverse clinical manifestations of BSLE, lupus nephritis, and hematologic involvement remain poorly understood. Further studies are justified to explain these mechanisms and validate their roles in disease progression.

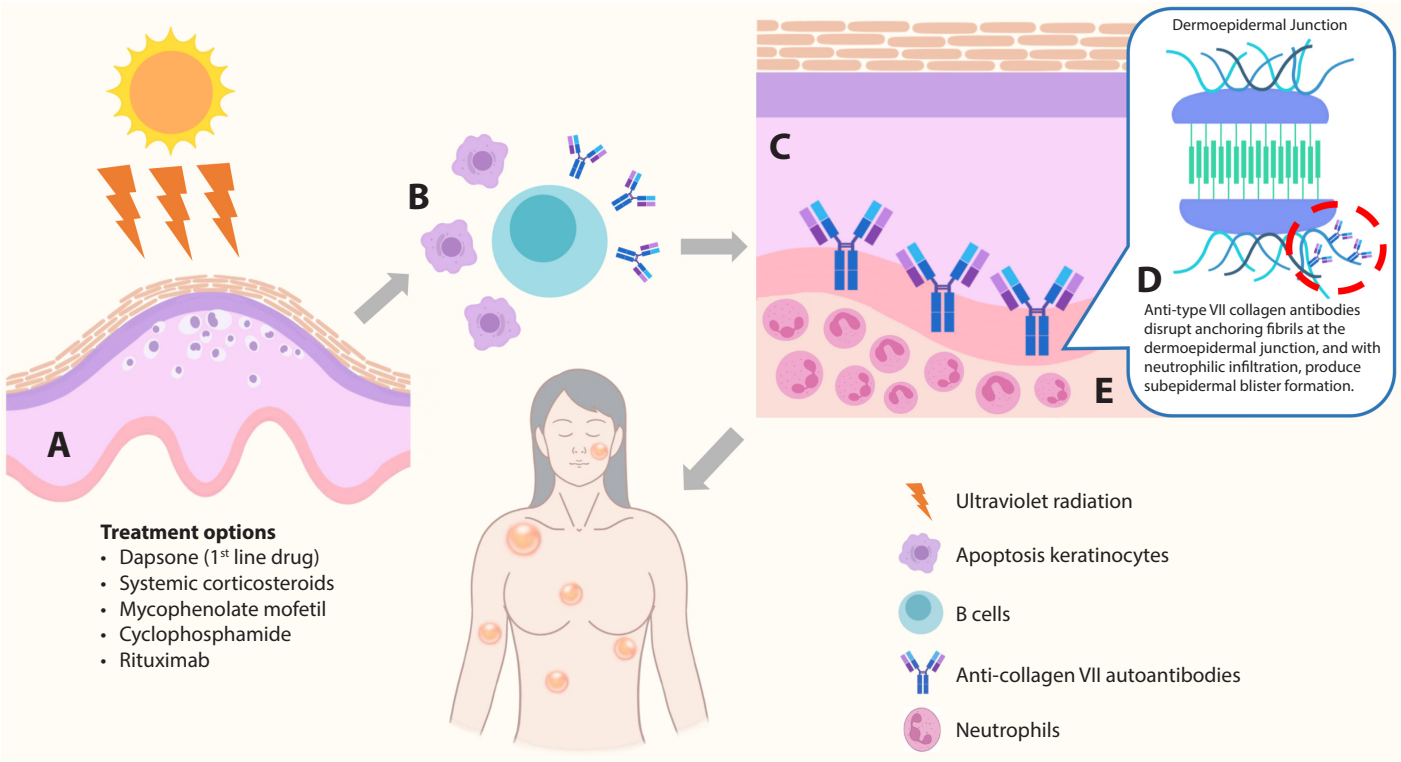

Figure 1. Ultraviolet radiation induces keratinocyte apoptosis, leading to the release of intracellular antigens. (A) Impaired clearance results in prolonged exposure of apoptotic material, promoting the generation of autoantibodies, including those targeting type VII collagen. (B) Autoantibody binding to anchoring fibrils at the dermoepidermal junction, leading to direct damage of type VII collagen, a key structural component anchoring the epidermal and dermal layers of the skin (C, D) Together with neutrophilic infiltration (E), this process results in subepidermal blister formation (F) characteristic of bullous systemic lupus erythematosus. Concurrent production of nitric oxide and proinflammatory cytokines facilitates neutrophil recruitment. In terms of treatment, dapsone is the first-line therapy for BSLE. If dapsone is contraindicated or not well tolerated, systemic corticosteroids, mycophenolate mofetil, cyclophosphamide, or rituximab may be considered as alternative options.

Clinical manifestations

Cutaneous involvement is observed in approximately 70-85% of patients with SLE and encompasses both lupus-specific and lupus-nonspecific lesions, as classified by Gilliam and Sontheimer.[38] **Figure 2** illustrates lupus-specific cutaneous lesions. Acute CLE features the classic malar rash and widespread maculopapular eruptions. Subacute CLE presents with annular or papulosquamous lesions, and neonatal lupus erythematosus most often manifests on the face. Chronic CLE, most commonly discoid lupus erythematosus, is characterized by scaly, indurated plaques that may result in scarring and dyspigmentation. Additional variants include BSLE and Rowell syndrome-like erythema multiforme, both of which are also considered lupus-specific lesions.[39] Clinically, it is characterized by the sudden onset of tense vesicles and bullae that may develop on either normal-appearing skin or erythematous, infiltrated areas (**Figure 3**).[22,26,40] However, the majority of cases (75-90%) indicated that BSLE lesions more frequently occur on erythematous skin.[16,23] Lesions in BSLE can affect both sun-exposed and sun-protected areas, with a predilection for the extremities, face, and trunk.[16] Additional involved sites include the neck, supraclavicular regions, and axillary folds. Although generalized distribution has been reported, it is relatively uncommon.[16] Mucosal involvement occurs in approximately 30-50% of cases, most frequently affecting the oral mucosa, particularly the labial and perioral regions, though genital involvement has also been documented.[16,22,41] Bullae generally progress to erosions and crusts, healing without scarring or milia formation, though residual hypopigmentation or, less frequently, hyperpigmentation may persist.[16,22,41] Pruritus is usually absent or mild.[40,42] Compared with previous cohorts, this study showed a more balanced sex distribution and older age at diagnosis, indicating that BSLE should be considered even in older and male patients presenting with tense bullae. (**Table 3**)

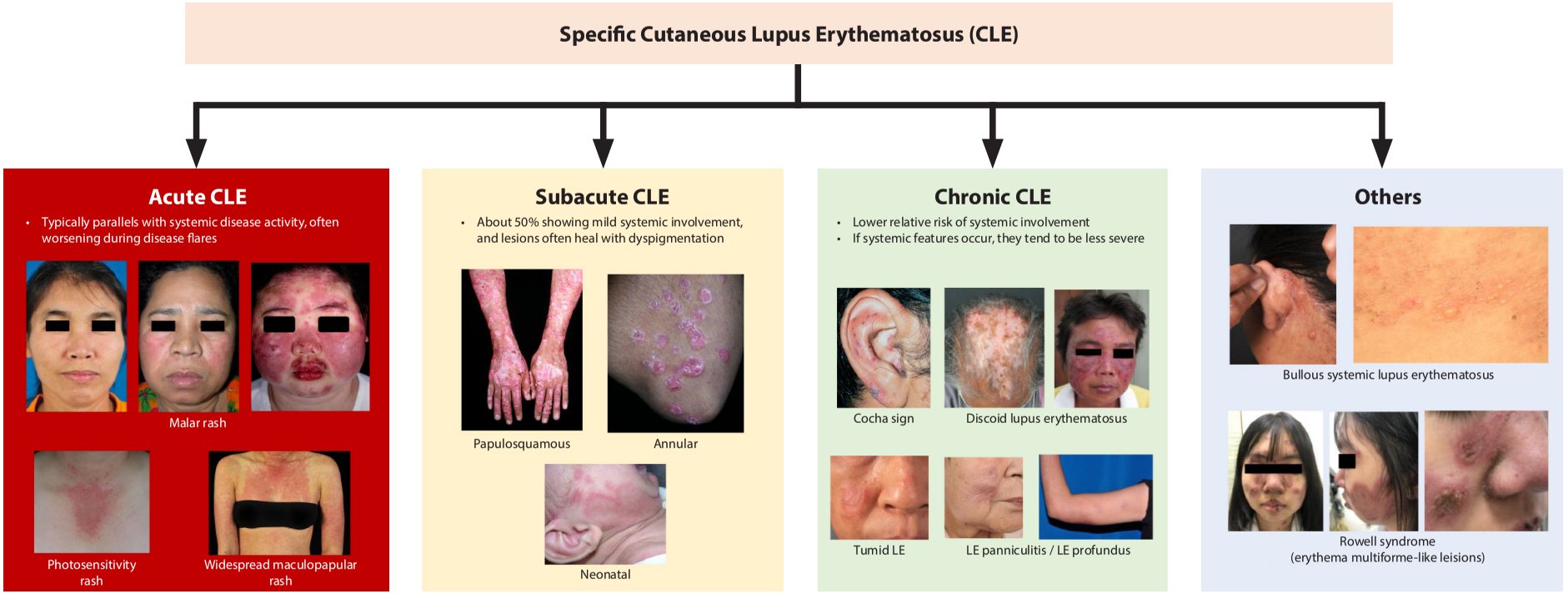

Figure 2. Representative clinical presentations of specific cutaneous lupus erythematosus.

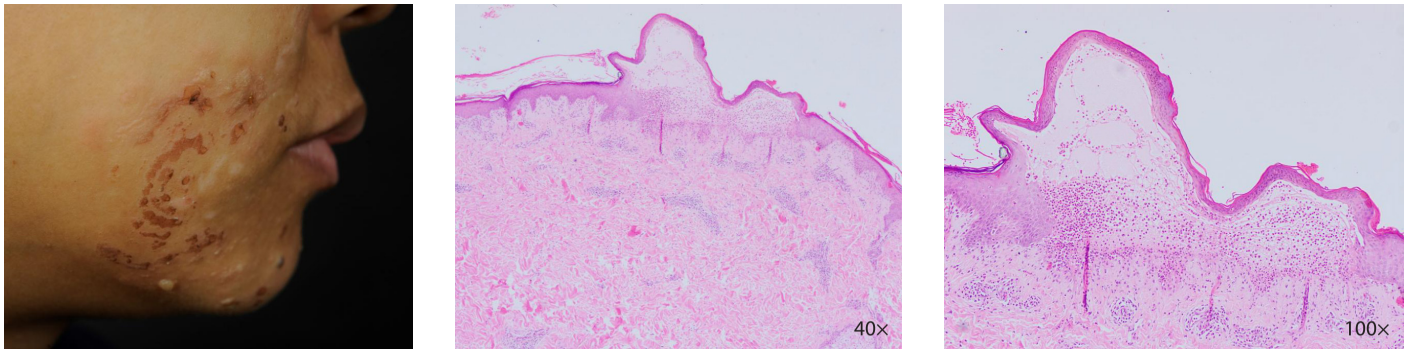

Figure 3. Bullous systemic lupus erythematosus typically presents with tense bullae that progress into erosions and crusts, healing without scarring or milia formation. Post-inflammatory pigmentary changes, including hypo- and hyperpigmentation, are usually observed after resolution. Histopathologic examination reveals subepidermal blister formation with a predominant neutrophilic infiltrate.

Table 3. Comparison of demographic characteristics, clinical distribution, and systemic involvement in patients with bullous systemic lupus erythematosus across published cohorts

Patient characteristics	This study (n = 12)	Chanprapaph K, et al. (n = 10)	Qiao L, et al. (n = 12)	de Risi-Pugliese T, et al. (n = 10)	Pons-Estel GJ, et al. (n = 6)
Country	Thailand	Thailand	China	France	Argentina
Published Year	-	2017	2022	2018	2018
Sex					
Female	6 (50%)	10 (100%)	10 (83.3%)	10 (100%)	6 (100%)
Age at diagnosis (years)	39.5#	24*	25.9#	24*	24*
Distribution					
Head and neck	4 (33.3%)	7 (70%)	10 (83.3%)	7 (70%)	NA
Trunk	4 (33.3%)	7 (70%)	7 (58.3%)	10 (100%)	
Upper extremities	8 (66.7%)	8 (80%)	8 (66.7%)	8 (80%)	
Lower extremities	6 (50%)		7 (58.3%)	5 (50%)	
Mucous membrane involvement	4 (33.3%)	5 (50%)	6 (50%)	6 (60%)	5 (83.3%)
Extra-cutaneous manifestations	9 (75%)	10 (100%)	12 (100%)	9 (90%)	6 (100%)
Lupus nephritis	8 (66.7%)	9 (90%)	11 (91.7%)	5 (55.6%)	5 (83.3%)
Cytopenia	7 (58.3%)	10 (10%)	10 (83.3%)	9 (100%)	6 (100%)
Arthritis	NA	4 (40%)	6 (50%)	5 (55.6%)	3 (50%)
Serositis	NA	4 (40%)	6 (50%)	0 (0%)	NA
Neuropsychiatric lupus	NA	0 (0%)	3 (25%)	2 (22.2%)	NA
Cardiac dysfunction	NA	NA	2 (16.7%)	NA	NA
Interstitial lung disease	NA	NA	1 (8.3%)	NA	NA
Gastrointestinal involvement	NA	NA	1 (8.3%)	NA	NA
Treatment outcomes (Complete or partial control)	11 (91.7%)	9 (90%)	9 (75%)	10 (100%)	
Steroid alone	1 (9.1%)	0 (0%)	1 (11.1%)	0 (0%)	
Steroid + dapsone	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	
Steroid + dapsone + AMD	1 (9.1%)	2 (22.2%)	0 (0%)	0 (0%)	
Steroid + dapsone + AMD + IS	2 (18.2%)	3 (33.3%)	0 (0%)	0 (0%)	
Steroid + AMD	1 (9.1%)	1 (11.1%)	0 (0%)	1 (10%)	NA
Steroid + AMD + IS	4 (36.4%)	3 (33.3%)	6 (66.7%)	0 (0%)	
Steroid + IS	0 (0%)	0 (0%)	2 (22.2%)	1 (10%)	
Dapsone alone	1 (9.1%)	0 (0%)	0 (0%)	5 (50%)	
Dapsone + IS	0 (0%)	0 (0%)	0 (0%)	1 (10%)	
Topical corticosteroid alone	0 (0%)	0 (0%)	0 (0%)	1 (10%)	
Anakinra	0 (0%)	0 (0%)	0 (0%)	1 (10%)	

Abbreviation: AMD, anti-malarial drugs; IS, immunosuppressants; NA, not available;
For age reporting, * indicates median values, and # indicates mean values.

The rarity of BSLE and early initiation of therapy leave its untreated natural course poorly documented. In this study, most patients developed bullous eruptions as the initial manifestation of SLE. The distribution and clinical characteristics of BSLE in pediatric patients are generally similar to those in adults.[43,44] Recurrence is uncommon, even among patients with ongoing systemic disease activity,[16,40] with reported relapse rates of approximately 20%.[23]

Systemic involvement

Similar to other subtypes of CLE, BSLE may occur independently of systemic disease activity; however, several reports have indicated an association between blistering and internal organ involvement, with rates ranging from 26% to 100%.[45] Renal involvement, manifesting as proteinuria, hematuria, and lupus nephritis, has been reported in approximately 50-90% of BSLE.[16,23,46-48] Hematologic involvement has been reported in approximately 50-80% of cases,[23] with some studies indicating rates as high as 100%.[16,46] Anemia is frequently observed,[16] though leukopenia predominates in Latin American and African cohorts.[46] In comparison, polyarthritis and serositis are less commonly observed in patients with BSLE, with reported frequencies of approximately 40-50%.[16,23] Neurological involvement has also been documented, occurring in about 25% of cases.[23] Regarding disease severity, patients with BSLE demonstrated significantly higher frequencies of renal and hematologic abnormalities, compared to SLE patients without bullous manifestations. These findings suggest that BSLE may serve as a clinical marker of more severe systemic disease in individuals with SLE.[23] As shown in **Table 3**, systemic involvement may be largely independent of population demographics, underscoring the need for careful systemic evaluation in clinical practice.

Serologic finding

At the time of BSLE diagnosis, ANA were the most frequently detected serologic marker. In one cohort, high-titer ANA at a dilution of ≥ 1:320 were observed in approximately 90% of cases.[16] Anti-dsDNA and anti-Smith antibodies were identified less frequently, with reported detection rates ranging from 30-60% and 15-30%, respectively, depending on the studies.[16] Additional autoantibodies such as anti-ribonucleoprotein, anti-Ro/SSA and anti-La/SSB may also be identified.[16] Inflammatory markers typically demonstrate elevation, with erythrocyte sedimentation rate increased, and complement levels were reduced in the majority of patients.[16]

Histopathology findings

Two distinct histopathologic patterns have been described in BSLE. The first resembles DH which is characterized by subepidermal blistering with a predominant neutrophilic infiltrate localized at the tips of the dermal papillae, forming microabscesses, along with nuclear debris (leukocytoclasia) and fibrin deposition. The second pattern features a dense, linear band of neutrophils aligned along the BMZ, often associated with subepidermal cleft and blister formation (**Figure 3**).[8,16,22,49] In more chronic or long-standing lesions, a mixed inflammatory infiltrate composed of both neutrophils and lymphocytes may extend into the deeper dermis.[50] Additional histologic features frequently observed include marked dermal edema, superficial and mid-dermal perivascular lymphocytic infiltration, and abundant mucin deposition within the reticular dermis.[50] Importantly, the histopathology of BSLE may mimic other subepidermal blistering disorders such as linear IgA dermatosis, or bullous pemphigoid. However, BSLE can be differentiated by several key features: the presence of neutrophilic nuclear dust, prominent mucin deposition in the reticular dermis, and the relative absence of eosinophils within the blister cavity.[42,50] These distinguishing characteristics serve as valuable diagnostic clues in the histopathologic evaluation of BSLE.

Immunofluorescence findings

Immunofluorescence is an important adjunctive diagnostic tool used alongside histopathological examination to support the diagnosis of BSLE. The immunopathologic hallmark of BSLE is the deposition of immunoreactants along the BMZ, demonstrated by DIF (**Figure 4**). In BSLE, DIF typically reveals multiple immunoreactant deposition at the BMZ, which may appear in pure linear, pure granular, or mixed linear and granular patterns.[51] In our study, mixed linear and granular deposits were observed in 33.3% of cases, pure granular in 41.7%, and pure linear in 25% of patients. IgG being the most frequently reported immunoreactant along the BMZ, detected in approximately 50-90% of cases.[23] The detection rates of other immunoreactants-such as IgA, IgM, and C3-vary across studies.[23] Compared to other forms of CLE, IgA deposition is more frequently observed in BSLE and correlates with the characteristic neutrophil-predominant inflammatory infiltrate seen histologically.[52,53] These deposits are often continuous and may extend into the dermis and perivascular regions.[51] DIF is also valuable in distinguishing BSLE from DH, in which IgA deposits in DH are localized to the dermal papillae rather than along the BMZ. In the salt-split skin technique, immunoreactant deposition in BSLE typically localizes to the dermal side, below the lamina densa, at the level of type VII collagen.[16,26] Nevertheless, this same pattern is also observed in epidermolysis bullosa acquisita (EBA), limiting its specificity.[54-56] Consequently, differentiating BSLE from EBA remains a key clinical challenge. In clinical practice, the diagnosis of BSLE is supported by integrating SLE-related clinical manifestations and serologic evidences, such as ANA, anti-dsDNA, and other relevant SLE serologies. Clinically, BSLE typically occurs in the setting of active SLE and often responds rapidly to lupus-directed therapy, whereas EBA tends to follow a more chronic and treatment-refractory course.[57] However, in certain circumstances, BSLE cannot be completely distinguished from EBA.

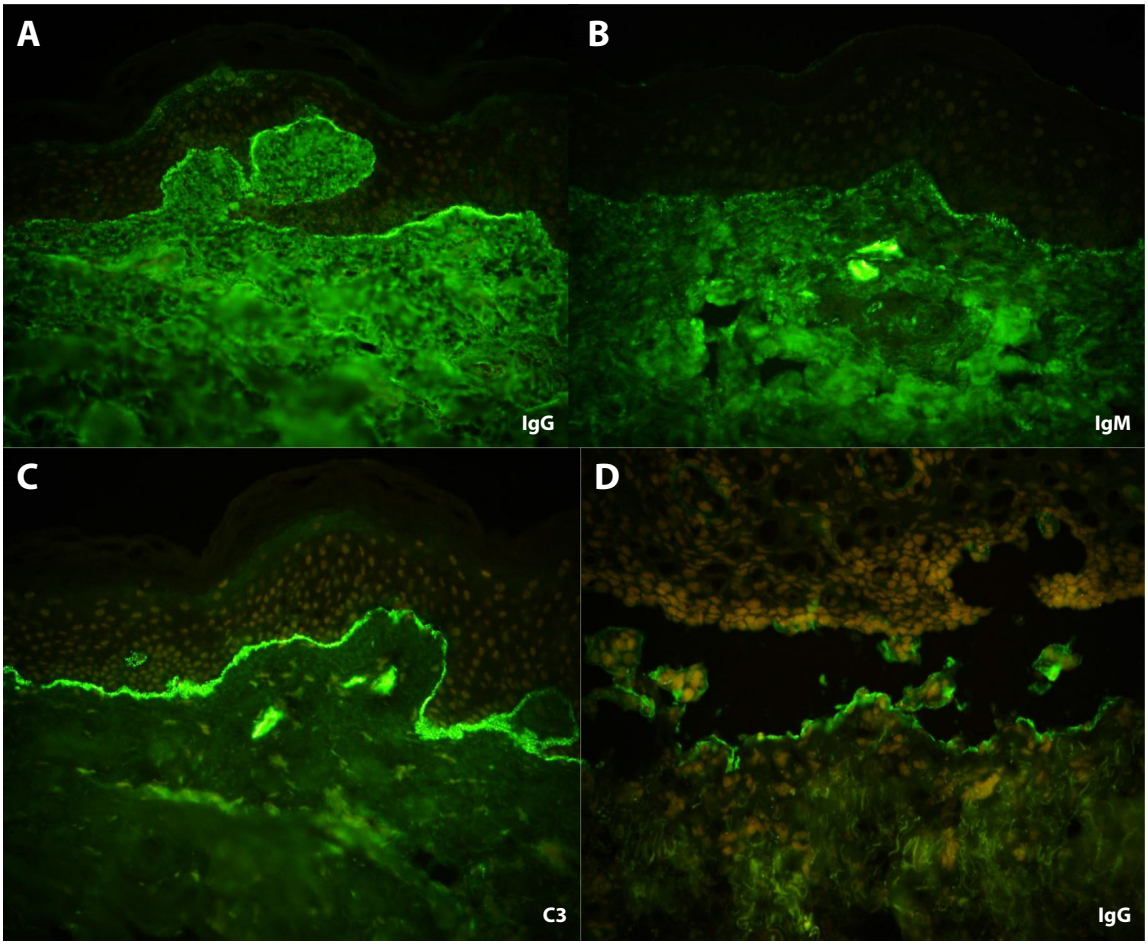

Figure 4. Direct immunofluorescence findings in bullous systemic lupus erythematosus demonstrate the deposition of multiple immunoglobulins (Ig) at the basement membrane zone (BMZ) including: (A) linear deposition of IgG along the BMZ; (B) granular deposition of IgM at the BMZ; (C) mixed linear and granular deposition of complement component C3 at the BMZ; and (D) immunoreactant deposition on the dermal side of the split, as shown by the salt-split skin technique. (20× magnification)

Enzyme-linked immunosorbent assays

Enzyme-linked immunosorbent assay (ELISA) has been developed to improve the diagnostic sensitivity and specificity of autoimmune bullous diseases.[58] ELISA can detect circulating autoantibodies against type VII collagen, specifically recognizing the 290- and 145-kDa fragments.[26] Notably, ELISA-based subclass analysis has shown that BSLE patients more frequently exhibit elevated levels of IgG2 and IgG3, whereas EBA is typically associated with IgG1 and IgG4 dominance.[26,59-63] Despite this advancement, ELISA testing does not yield positive results in all cases of BSLE, with previous reported positivity rates of approximately 60%.[23] This raises the possibility that other autoantigens may contribute to disease pathogenesis. Supporting this hypothesis, additional autoantibodies targeting laminin-5, laminin-6, and bullous pemphigoid antigen 1 have been identified in patients with BSLE.[64] This observation suggests the involvement of epitope spreading, wherein an initial autoimmune response directed against type VII collagen may subsequently expands to include other BMZ components.

Due to the heterogeneity of antigenic targets, BSLE has been immunopathologically classified into three subtypes based on autoantibody specificity, as determined by IIF, ELISA, or immunoelectron microscopy. Type I, the most common subtype, is characterized by the presence of autoantibodies against type VII collagen, either circulating in serum or deposited at the BMZ. Type II lacks these antibodies and is believed to target unidentified BMZ antigens. Type III may or may not show autoantibodies to type VII collagen, reflecting diagnostic heterogeneity.[23,26] However, the clinical relevance and diagnostic distinctions of these subtypes remain poorly defined.

Treatment / Management

In BSLE patients with active systemic involvement, treatment with systemic corticosteroids and/or immunosuppressive agents is required. In contrast, in patients without systemic involvement, bullous lesions may be managed with dapsone monotherapy or dapsone in combination with corticosteroids and/or immunosuppressive agents, depending on the severity of cutaneous disease. Therefore, dapsone may be initiated and assessed for response before escalating to immunosuppressive therapy in patients without widespread cutaneous involvement or systemic disease.

Dapsone has consistently shown rapid and reliable control of BSLE lesions and is widely considered the first-line treatment.[47,65] It has demonstrated rapid and marked clinical efficacy, with response rates reported in up to 90% of patients.[47] Improvement in skin lesions is frequently observed within a few days of initiating therapy.[66] Dapsone exhibits both antimicrobial and anti-inflammatory properties, the latter being the primary basis for its efficacy in neutrophilic dermatoses. Its anti-inflammatory activity is primarily attributed to the inhibition of neutrophil-mediated tissue damage. Key mechanisms include inactivation of myeloperoxidase, an enzyme essential for generating reactive oxygen species, resulting in reduced oxidative tissue damage.[65] Dapsone also suppresses neutrophil migration to extravascular sites by inhibiting adherence-dependent functions essential for neutrophil recruitment, further contributing to its anti-inflammatory effects.[67] Furthermore, dapsone impairs chemoattractant-induced signal transduction, thereby reducing neutrophil infiltration and local production of reactive oxygen species and proteolytic enzymes in affected skin, as observed in neutrophilic dermatoses.[68] Another proposed mechanism includes the inhibition of calcium-dependent neutrophil functions, particularly the release of tissue-damaging oxidants and proteases, contributing to its therapeutic efficacy in inflammatory skin disorders.[69] Given the neutrophil-predominant infiltrate characteristic of BSLE, this mechanism of action supports dapsone's efficacy in this condition. The initial recommended dose of dapsone is 50 mg per day.[65] Titration may be performed by increasing the dose in 25 mg increments weekly, guided by close laboratory monitoring.[65] The dosage can be increased up to a maximum of 200 mg per day, depending on clinical response and patient tolerability.[22] Prior to initiation, patients should be screened for glucose-6-phosphate dehydrogenase deficiency due to the risk of hemolysis. Hemolytic anemia may occur in up to 50% of patients, along with other adverse effects such as methemoglobinemia, agranulocytosis, hepatitis, and hypersensitivity reactions, including drug hypersensitivity syndrome.[70] Hemoglobin monitoring is recommended during the first month of therapy and every three months thereafter, with methemoglobin levels typically assessed between days 8 and 14 of treatment.[71] Notably, dapsone is considered safe for use during pregnancy and lactation.[71] In some cases of BSLE, dapsone therapy can be successfully discontinued within one year without recurrence of bullous lesions.[72,73] The reported success rate of dapsone in achieving cutaneous disease control varies across studies, ranging from 70% to 100%.[23]

If dapsone is contraindicated or poorly tolerated, systemic immunosuppressive agents, such as systemic corticosteroids, mycophenolate mofetil, or cyclophosphamide, may be employed either as monotherapy or in combination, particularly in patients with active systemic involvement or widespread cutaneous disease.[18,74] Intravenous immunoglobulin has been used in refractory BSLE, especially when immunosuppressants are contraindicated, though supporting evidence is limited to case reports.[74] Biologic therapy, particularly rituximab, has shown promise in the management of refractory BSLE. As a monoclonal antibody targeting CD20 on B lymphocytes, rituximab has demonstrated efficacy in cases unresponsive to conventional immunosuppressive agents.[65,75-77] In addition, belimumab, a monoclonal antibody directed against B-lymphocyte stimulator, has been employed in a BSLE patient based on its approved indication for SLE.[78] However, evidence supporting their use in BSLE is currently limited to a single case report, and further studies are warranted to evaluate its therapeutic role in this subset.

Conclusion

Despite being recognized for several decades, BSLE remains poorly understood due to its rarity, with most existing data derived from isolated case reports and small case series. Data are particularly limited in Southeast Asia. This study reports findings from a Thai cohort, which may help bridge regional knowledge gaps and underscore the need for larger, prospective studies to advance understanding of BSLE. Nevertheless, several limitations should be acknowledged, including its retrospective design and relatively small sample size, which may affect the generalizability of the findings. Further prospective, multicenter studies involving larger patient cohorts are warranted.

Acknowledgment

The authors gratefully acknowledge Dr. Pariya Pinkeaw, MD, for her valuable assistance and for creating the beautifully illustrated figures that significantly enhanced this manuscript.

Conflict of interests

The authors declare that they have no potential conflicts of interest related to the present study.

Authors' contributions

- CR, KK, PT, and LC contributed to the conceptualization of the study.
- CR, SN, MJ, and LC were responsible for data curation.
- CR and LC performed the formal analysis.
- CR and LC prepared the original draft.
- CR, KK, PT, and LC reviewed and edited the manuscript.

References

1. Stull C, Sprow G, Werth VP. Cutaneous Involvement in Systemic Lupus Erythematosus: A Review for the Rheumatologist. J Rheumatol. 2023; 50(1):27-35.
2. Sontheimer RD. The lexicon of cutaneous lupus erythematosus--a review and personal perspective on the nomenclature and classification of the cutaneous manifestations of lupus erythematosus. Lupus. 1997;6(2): 84-95.
3. Rothfield N, Sontheimer RD, Bernstein M. Lupus erythematosus: systemic and cutaneous manifestations. Clin Dermatol. 2006;24(5):348-62.
4. Jarukitsopa S, Hoganson DD, Crowson CS, Sokumbi O, Davis MD, Michet CJ, Jr., et al. Epidemiology of systemic lupus erythematosus and cutaneous lupus erythematosus in a predominantly white population in the United States. Arthritis Care Res (Hoboken). 2015;67(6):817-28.
5. Durosaro O, Davis MD, Reed KB, Rohlinger AL. Incidence of cutaneous lupus erythematosus, 1965-2005: a population-based study. Arch Dermatol. 2009;145(3):249-53.

6. Izmirly P, Buyon J, Belmont HM, Sahl S, Wan I, Salmon J, et al. Population-based prevalence and incidence estimates of primary discoid lupus erythematosus from the Manhattan Lupus Surveillance Program. Lupus Sci Med. 2019;6(1):e000344.
7. Drenkard C, Parker S, Aspey LD, Gordon C, Helmick CG, Bao G, et al. Racial Disparities in the Incidence of Primary Chronic Cutaneous Lupus Erythematosus in the Southeastern US: The Georgia Lupus Registry. Arthritis Care Res (Hoboken). 2019;71(1):95-103.
8. Yell JA, Allen J, Wojnarowska F, Kirtschig G, Burge SM. Bullous systemic lupus erythematosus: revised criteria for diagnosis. Br J Dermatol. 1995;132(6):921-8.
9. Thomas JR, 3rd, Su WP. Concurrence of lupus erythematosus and dermatitis herpetiformis. A report of nine cases. Arch Dermatol. 1983; 119(9):740-5.
10. Moncada B. Dermatitis herpetiformis in association with systemic lupus erythematosis. Arch Dermatol. 1974;109(5):723-5.
11. Aronson AJ, Soltani K, Aronson IK, Ong RT. Systemic lupus erythematosus and dermatitis herpetiformis: concurrence with Marfan's syndrome. Arch Dermatol. 1979;115(1):68-70.
12. Clayton CA, Burnham TK. Systemic lupus erythematosus and coexisting bullous pemphigoid: immunofluorescent investigations. J Am Acad Dermatol. 1982;7(2):236-45.
13. Stoll DM, King LE, Jr. Association of bullous pemphigoid with systemic lupus erythematosus. Arch Dermatol. 1984;120(3):362-6.
14. Szabó E, Husz S, Kovács L. Coexistent atypical bullous pemphigoid and systemic lupus erythematosus. Br J Dermatol. 1981;104(1):71-5.
15. Cruz PD, Jr., Coldiron BM, Sontheimer RD. Concurrent features of cutaneous lupus erythematosus and pemphigus erythematosus following myasthenia gravis and thymoma. J Am Acad Dermatol. 1987;16(2 Pt 2): 472-80.
16. Chanprapaph K, Sawatwarakul S, Vachiramon V. A 12-year retrospective review of bullous systemic lupus erythematosus in cutaneous and systemic lupus erythematosus patients. Lupus. 2017;26(12):1278-84.
17. Bernard P, Vaillant L, Labeille B, Bedane C, Arbeille B, Denoeux JP, et al. Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. Arch Dermatol. 1995;131(1):48-52.
18. Duan L, Chen L, Zhong S, Wang Y, Huang Y, He Y, et al. Treatment of Bullous Systemic Lupus Erythematosus. J Immunol Res. 2015;2015: 167064.
19. Siddig O, Mustafa MB, Kordofani Y, Gibson J, Suleiman AM. The epidemiology of autoimmune bullous diseases in Sudan between 2000 and 2016. PLoS One. 2021;16(7):e0254634.
20. Wong SN, Chua SH. Spectrum of subepidermal immunobullous disorders seen at the National Skin Centre, Singapore: a 2-year review. Br J Dermatol. 2002;147(3):476-80.
21. Lourenço DM, Gomes RC, Aikawa NE, Campos LM, Romiti R, Silva CA. Childhood-onset bullous systemic lupus erythematosus. Lupus. 2014; 23(13):1422-5.
22. Vale E, Garcia LC. Cutaneous lupus erythematosus: a review of etiopathogenic, clinical, diagnostic and therapeutic aspects. An Bras Dermatol. 2023;98(3):355-72.
23. Qiao L, Zhang B, Zheng W, Li M, Zhao Y, Zeng X, et al. Clusters of clinical and immunologic features in patients with bullous systemic lupus erythematosus: experience from a single-center cohort study in China. Orphanet J Rare Dis. 2022;17(1):290.
24. Kuhn A, Herrmann M, Kleber S, Beckmann-Welle M, Fehsel K, Martin-Villalba A, et al. Accumulation of apoptotic cells in the epidermis of patients with cutaneous lupus erythematosus after ultraviolet irradiation. Arthritis Rheum. 2006;54(3):939-50.
25. Muñoz LE, Lauber K, Schiller M, Manfredi AA, Herrmann M. The role of defective clearance of apoptotic cells in systemic autoimmunity. Nat Rev Rheumatol. 2010;6(5):280-9.
26. Contestable JJ, Edhegard KD, Meyerle JH. Bullous systemic lupus erythematosus: a review and update to diagnosis and treatment. Am J Clin Dermatol. 2014;15(6):517-24.
27. Haas PJ, van Strijp J. Anaphylatoxins: their role in bacterial infection and inflammation. Immunol Res. 2007;37(3):161-75.
28. Mayadas TN, Tsokos GC, Tsuboi N. Mechanisms of immune complex-mediated neutrophil recruitment and tissue injury. Circulation. 2009;120(20):2012-24.
29. Lupia E, Del Sorbo L, Bergerone S, Emanuelli G, Camussi G, Montrucchio G. The membrane attack complex of complement contributes to plasmin-induced synthesis of platelet-activating factor by endothelial cells and neutrophils. Immunology. 2003;109(4):557-63.
30. Bachmann M, Waibler Z, Pleli T, Pfeilschifter J, Mühl H. Type I Interferon Supports Inducible Nitric Oxide Synthase in Murine Hepatoma Cells and Hepatocytes and during Experimental Acetaminophen-Induced Liver Damage. Front Immunol. 2017;8:890.
31. Costa VM, Torres KC, Mendonça RZ, Gresser I, Gollob KJ, Abrahamsohn IA. Type I IFNs stimulate nitric oxide production and resistance to Trypanosoma cruzi infection. J Immunol. 2006;177(5): 3193-200.
32. Postal M, Vivaldo JF, Fernandez-Ruiz R, Paredes JL, Appenzeller S, Niewold TB. Type I interferon in the pathogenesis of systemic lupus erythematosus. Curr Opin Immunol. 2020;67:87-94.
33. Wanchu A, Khullar M, Deodhar SD, Bambery P, Sud A. Nitric oxide synthesis is increased in patients with systemic lupus erythematosus. Rheumatol Int. 1998;18(2):41-3.
34. Hendel N, Akmatov MK, Hamel J, Vogelberg C, Pessler F. Exhaled breath analysis in childhood rheumatic disorders--a longitudinal study. J Breath Res. 2016;10(2):021001.
35. Rönnblom L, Leonard D. Interferon pathway in SLE: one key to unlocking the mystery of the disease. Lupus Sci Med. 2019;6(1):e000270.
36. Baechler EC, Batliwalla FM, Karypis G, Gaffney PM, Ortmann WA, Espe KJ, et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc Natl Acad Sci U S A. 2003;100(5):2610-5.
37. Kirou KA, Lee C, George S, Louca K, Peterson MG, Crow MK. Activation of the interferon-alpha pathway identifies a subgroup of systemic lupus erythematosus patients with distinct serologic features and active disease. Arthritis Rheum. 2005;52(5):1491-503.
38. Grönhagen CM, Nyberg F. Cutaneous lupus erythematosus: An update. Indian Dermatol Online J. 2014;5(1):7-13.
39. Elmgren J, Nyberg F. Clinical aspects of cutaneous lupus erythematosus. Front Med (Lausanne). 2022;9:984229.
40. Rutnin S, Chanprapaph K. Vesiculobullous diseases in relation to lupus erythematosus. Clin Cosmet Investig Dermatol. 2019;12:653-67.
41. Nico MM, Lourenço SV. Multiple blisters along the lip vermilion are a clue to bullous lupus erythematosus. Acta Derm Venereol. 2012; 92(4):404-5.
42. Gammon WR, Briggaman RA. Bullous SLE: a phenotypically distinctive but immunologically heterogeneous bullous disorder. J Invest Dermatol. 1993;100(1):28s-34s.
43. Torres Saavedra FA, Campo LR, Mendez MV, Barreneche NM, Suaza GAV, Restrepo JDR, et al. Bullous lupus as the first manifestation of systemic lupus erythematosus in the pediatric population: A diagnostic challenge in daily practice. Lupus. 2020;29(14):1937-42.
44. Hasbún ZM, Rollan MP, Chaparro RX, Fischer SC, Castrillón VA, González BS, et al. Bullous systemic lupus erythematosus: An uncommon manifestation in pediatric population. Andes Pediatr. 2021;92(3):428-33.
45. Pons-Estel BA, Catoggio LJ, Cardiel MH, Soriano ER, Gentiletti S, Villa AR, et al. The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among "Hispanics". Medicine (Baltimore). 2004;83(1):1-17.
46. Pons-Estel GJ, Quintana R, Alarcón GS, Sacnún M, Ugarte-Gil MF, Pons-Estel BA. A 12-year retrospective review of bullous systemic lupus erythematosus in cutaneous and systemic lupus erythematosus patients. Lupus. 2018;27(10):1753-4.
47. de Risi-Pugliese T, Cohen Aubart F, Haroche J, Moguelet P, Grootenboer-Mignot S, Mathian A, et al. Clinical, histological, immunological presentations and outcomes of bullous systemic lupus erythematosus: 10 New cases and a literature review of 118 cases. Semin Arthritis Rheum. 2018;48(1):83-9.
48. Ugarte-Gil MF, Fuentes-Silva Y, Pimentel-Quiroz VR, Pons-Estel GJ, Quintana R, Pons-Estel BA, et al. Global excellence in rheumatology in Latin America: The case of systemic lupus erythematosus. Front Med (Lausanne). 2022;9:988191.
49. Bitar C, Menge TD, Chan MP. Cutaneous manifestations of lupus erythematosus: a practical clinicopathological review for pathologists. Histopathology. 2022;80(1):233-50.
50. Baltaci M, Fritsch P. Histologic features of cutaneous lupus erythematosus. Autoimmun Rev. 2009;8(6):467-73.

51. Vassileva S. Bullous systemic lupus erythematosus. Clin Dermatol. 2004;22(2):129-38.
52. Malik AM, Tupchong S, Huang S, Are A, Hsu S, Motaparthi K. An Updated Review of Pemphigus Diseases. Medicina (Kaunas). 2021;57(10).
53. Barbosa WS, Rodarte CM, Guerra JG, Maciel VG, Fleury Júnior LF, Costa MB. Bullous systemic lupus erythematosus: differential diagnosis with dermatitis herpetiformis. An Bras Dermatol. 2011;86(4 Suppl 1): S92-5.
54. Rujitharanawong C, Kulthanan K, Tuchinda P, Pinkaew S, Chanchaemsri N, Nuttawong S, et al. Direct Immunofluorescence in Cutaneous and Systemic Lupus Erythematosus: A Literature Review. Siriraj Medical Journal. 2023;75(2):145-66.
55. Aoki V, Sousa JX, Jr., Fukumori LM, Périgo AM, Freitas EL, Oliveira ZN. Direct and indirect immunofluorescence. An Bras Dermatol. 2010;85(4):490-500.
56. Obermoser G, Sontheimer RD, Zelger B. Overview of common, rare and atypical manifestations of cutaneous lupus erythematosus and histopathological correlates. Lupus. 2010;19(9):1050-70.
57. Kridin K, Kneiber D, Kowalski EH, Valdebran M, Amber KT. Epidermolysis bullosa acquisita: A comprehensive review. Autoimmun Rev. 2019;18(8):786-95.
58. Komorowski L, Müller R, Vorobyev A, Probst C, Recke A, Jonkman MF, et al. Sensitive and specific assays for routine serological diagnosis of epidermolysis bullosa acquisita. J Am Acad Dermatol. 2013;68(3):e89-95.
59. Gual A, Guilabert A, Iranzo P, Flores G, Diaz LA, Mascaró JM, Jr. IgG autoantibody subclass analysis as a tool to differentiate epidermolysis bullosa acquisita with overlapping features of bullous systemic lupus erythematosus. J Am Acad Dermatol. 2013;69(1):e34-6.
60. Recke A, Sitaru C, Vidarsson G, Evensen M, Chiriac MT, Ludwig RJ, et al. Pathogenicity of IgG subclass autoantibodies to type VII collagen: induction of dermal-epidermal separation. J Autoimmun. 2010;34(4): 435-44.
61. Herrero-González JE, Mascaró JM, Jr., Herrero C, Dilling A, Zillikens D, Sitaru C. Autoantibodies from patients with BSLE inducing recruitment of leukocytes to the dermoepidermal junction and subepidermal splits in cryosections of human skin. Arch Dermatol. 2006;142(11):1513-6.
62. Bernard P, Prost C, Aucouturier P, Durepaire N, Denis F, Bonnetblanc JM. The subclass distribution of IgG autoantibodies in cicatricial pemphigoid and epidermolysis bullosa acquisita. J Invest Dermatol. 1991;97(2):259-63.
63. Oostingh GJ, Sitaru C, Zillikens D, Kromminga A, Lührs H. Subclass distribution of type VII collagen-specific autoantibodies in patients with inflammatory bowel disease. J Dermatol Sci. 2005;37(3):182-4.
64. Chan LS, Lapiere JC, Chen M, Traczyk T, Mancini AJ, Paller AS, et al. Bullous systemic lupus erythematosus with autoantibodies recognizing multiple skin basement membrane components, bullous pemphigoid antigen 1, laminin-5, laminin-6, and type VII collagen. Arch Dermatol. 1999;135(5):569-73.
65. Sprow G, Afarideh M, Dan J, Hedberg ML, Werth VP. Bullous systemic lupus erythematosus in females. Int J Womens Dermatol. 2022;8(3):e034.
66. Hall RP, Lawley TJ, Smith HR, Katz SI. Bullous eruption of systemic lupus erythematosus. Dramatic response to dapsone therapy. Ann Intern Med. 1982;97(2):165-70.
67. Booth SA, Moody CE, Dahl MV, Herron MJ, Nelson RD. Dapsone suppresses integrin-mediated neutrophil adherence function. J Invest Dermatol. 1992;98(2):135-40.
68. Debol SM, Herron MJ, Nelson RD. Anti-inflammatory action of dapsone: inhibition of neutrophil adherence is associated with inhibition of chemoattractant-induced signal transduction. J Leukoc Biol. 1997;62(6):827-36.
69. Suda T, Suzuki Y, Matsui T, Inoue T, Niide O, Yoshimaru T, et al. Dapsone suppresses human neutrophil superoxide production and elastase release in a calcium-dependent manner. Br J Dermatol. 2005; 152(5):887-95.
70. Fairley JL, Oon S, Saracino AM, Nikpour M. Management of cutaneous manifestations of lupus erythematosus: A systematic review. Semin Arthritis Rheum. 2020;50(1):95-127.
71. Chasset F, Francès C. Current Concepts and Future Approaches in the Treatment of Cutaneous Lupus Erythematosus: A Comprehensive Review. Drugs. 2019;79(11):1199-215.
72. Yung A, Oakley A. Bullous systemic lupus erythematosus. Australas J Dermatol. 2000;41(4):234-7.
73. Grover C, Khurana A, Sharma S, Singal A. Bullous systemic lupus erythematosus. Indian J Dermatol. 2013;58(6):492.
74. Chow KW, Sweis JJG, Alawneh D, Jetanalin P, Ascoli C, Kuschel S, et al. Bullous Systemic Lupus Erythematosus Successfully Treated With Intravenous Immunoglobulin and Mycophenolate Mofetil. Cureus. 2023;15(9):e45800.
75. Alsanafi S, Kovarik C, Mermelstein AL, Werth VP. Rituximab in the treatment of bullous systemic lupus erythematosus. J Clin Rheumatol. 2011;17(3):142-4.
76. Lowe CD, Brahe CA, Green B, Lam TK, Meyerle JH. Bullous systemic lupus erythematosus successfully treated with rituximab. Cutis. 2019;103(6):E5-e7.
77. Ratanapokasatit Y, Seree-Aphinan C, Chanprapaph K. Refractory Bullous Systemic Lupus Erythematosus Successfully Treated with Rituximab: A Case Report and Literature Review. Clin Cosmet Investig Dermatol. 2023;16:883-90.
78. Zeng HQ, Lu XP, Yan ZB, Ye ZZ. First case presentation of refractory pediatric bullous lupus erythematosus (BSLE) treatment with belimumab. Eur Rev Med Pharmacol Sci. 2022;26(21):7980-5.
79. Grönhagen CM, Fored CM, Granath F, Nyberg F. Cutaneous lupus erythematosus and the association with systemic lupus erythematosus: a population-based cohort of 1088 patients in Sweden. Br J Dermatol. 2011;164(6):1335-41.