BULLOUS SYSTEMIC LUPUS ERYTHEMATOSUS: A CASE SERIES AND 5-YEAR RETROSPECTIVE REVIEW

Hoang Quoc Tuan[1,*], Hoang Thi Phuong[2], Dang Thi Luong[2], Hoang Van Tam[2,3]

ABSTRACT

Bullous systemic lupus erythematosus (BSLE) is a rare presentation of systemic lupus erythematosus (SLE) that mainly occurs in females (30 - 40 years old) and less frequently in children and adolescents. BSLE has many clinical and histological feautures that may lead to misdiagnosis and delayed treatment.

We report 14 patients with blistering lesions at admission, who were diagnosed with BSLE over the last 5 years in The National Hospital of Dermatology and Venereology (NHDV), Vietnam. Our cases were reviewed carefully of the clinical presentation, histopathology, immunofluorescence and therapeutic regimens. Because these manifestations may be confused with several other blistering diseases, such as bullous pemphigoid (BP), dermatitis herpetiformis (DH) or epidermolysis bullosa acquisita (EBA). All of our cases presented with the rapid and widespread development of tense vesicles and bullae over erythematous macules or plaques predominantly on the face, neck, upper extremities and trunk with symmetrical distribution. Mucosal involvement is common on oral and genital areas. The lesions usually progress without scarring and milia, but hypo or hyperchromia may be present. These cases shared the histopathology in common with a subepidermal bullae with neutrophil-predominant inflammatory infiltrate below the bullae formation. Both the direct and indirect immunofluorescence findings were made to confirm the diagnosis of BSLE. Some of our cases were well-responded to treatment with dapson, but several ones required systemic corticosteroids and immunosuppressants. We emphasize the relevance of recognizing BSLE - a rare presentation of SLE - which may evolve with marked clinical presentation.

Keywords: *Bullous systemic lupus erythematosus, BSLE, Dapsone.*

1. INTRODUCTION

Bullous systemic lupus erythematosus (BSLE) is a rare subepidermal blistering disorder, accounting for less than 5% of systemic lupus erythematosus (SLE) cases. This condition is more commonly seen in young women aged 20 - 40 years[1-3], with lower incidence in men and children. Most patients diagnosed with BSLE have previously been diagnosed with SLE; however, in some cases-particularly in children-BSLE may be the initial manifestation[3-5], complicating diagnosis and treatment. There have been reports linking BSLE to SLE flare-ups,

[1]Central Military Hospital 108
[2]National Hospital of Dermatology and Venereology
[3]Hanoi Medical University
**Correspondence: Email: hoangquoctuanyhn@gmail.com*
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particularly with lupus nephritis, highlighting the importance of early diagnosis to prevent severe complications such as organ damage from SLE[6,7].

The pathogenesis of BSLE involves autoantibodies against NC1 and NC2 (non-collagenous type 1 and 2) of type VII collagen in anchoring fibrils, which are crucial components connecting the lamina densa and the dermis[1,8]. Additionally, autoantibodies against laminin 322, laminin 311, or pemphigoid blistering antigen type 1 have been identified[1,9]. These factors result in a clinical presentation characterized by vesicular lesions and tense bullae, making it difficult to distinguish from other subepidermal blistering disorders such as acquired epidermolysis bullosa (EBA), dermatitis herpetiformis (DH), or bullous pemphigoid (BP).

We report 14 cases diagnosed with BSLE at the Central Dermatology Hospital over a 5-year period from 2018 to 2023. The cases were carefully analyzed regarding clinical features, histopathology, and immunofluorescence, as well as treatment response and follow-up for recurrence risk.

2. CLINICAL CASES

2.1. Clinical manifestations

Table 1 summarizes the clinical characteristics and related factors of the 14 patients.

Table 1. Clinical characteristics and related factors of 14 BSLE patients

No.	Patient Name	Gender	Age	SLE History	Mucocutaneous Lesions			Kidney Lesions
					Tense bullae	Urticarial wheals	Mucosal erosions in the mouth	
1	Nguyễn Thị N.	Female	40	Present	Present	Absent	Present	Present
2	Lữ Bảo Y.	Female	21	Present	Present	Absent	Absent	Absent
3	Võ Thị H.	Female	45	Present	Present	Present	Present	Present
4	Hoàng Thị H.	Female	8	Absent	Present	Present	Present	Absent
5	Đinh Thế T.	Male	5	Absent	Present	Present	Absent	Present
6	Tráng Thị X.	Female	11	Absent	Present	Absent	Absent	Absent
7	Lê Tuyên N.	Male	27	Present	Present	Present	Present	Absent
8	Vi Văn Đ.	Male	21	Present	Present	Present	Present	Absent
9	Lưu Thị T.	Female	50	Absent	Present	Present	Present	Absent
10	Trương Văn P.	Male	62	Absent	Present	Present	Present	Present
11	Nguyễn Mai L.	Female	12	Present	Present	Present	Present	Present
12	Đinh Thị T.	Female	39	Present	Present	Absent	Present	Present
13	Nguyễn Thị Hải Y.	Female	21	Present	Present	Present	Absent	Present
14	Trần Thị Hồng T.	Female	22	Present	Present	Present	Absent	Absent

Among the 14 BSLE cases, females predominated with 10 patients (71.4%), compared to 4 male patients (28.6%). The average age of the patients was 27.4 years, with 50% of patients in the 20 - 40 age group; there were 4 pediatric patients (28.6%). The youngest patient was 5 years old, while the oldest was 62. Nine patients had been previously diagnosed with SLE, accounting for 64.3%, while the remaining 5 patients (35.7%) presented with BSLE as the initial manifestation. All patients exhibited clinical lesions characterized by vesicles and tense bullae that appeared suddenly on a background of erythema or healthy skin, primarily concentrated on the face, neck, trunk, and upper limbs. Additionally, 71.4% of patients had urticarial wheal-like lesions, and 64.3% experienced mucosal erosions in the mouth. Fifty percent of patients presented with kidney lesions.

Figure 1 shows the clinical lesions of patient number 12, Đinh Thị T.

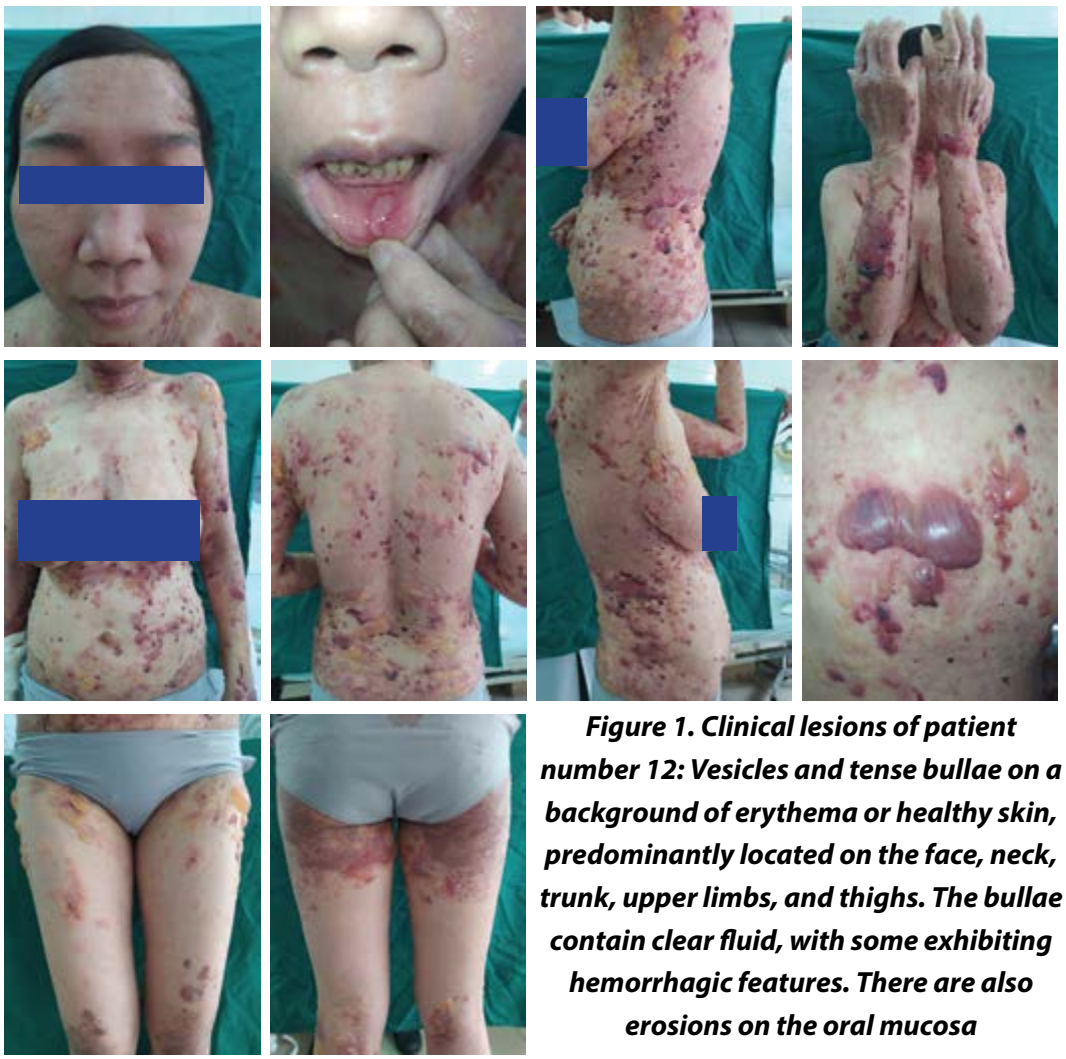

Figure 1. Clinical lesions of patient number 12: Vesicles and tense bullae on a background of erythema or healthy skin, predominantly located on the face, neck, trunk, upper limbs, and thighs. The bullae contain clear fluid, with some exhibiting hemorrhagic features. There are also erosions on the oral mucosa

2.2. Histopathological features

The patients underwent biopsies of the bullous lesions, which were stained with hematoxylin and eosin (H&E) for histopathological examination. Below is the histopathological image of patient number 12.

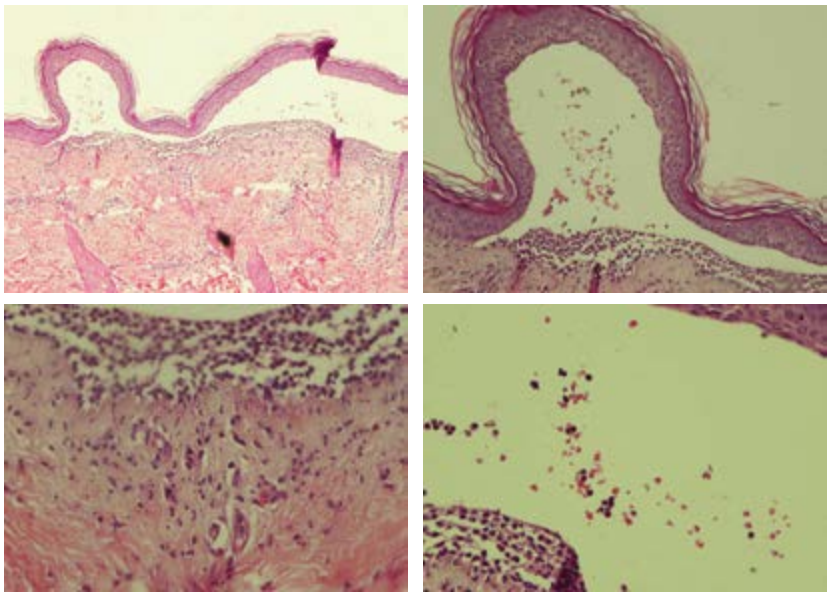

Figure 2. Histopathological image stained with H&E of patient number 12: Subepithelial bullae with significant infiltration of neutrophils

100% of patients exhibited a common histopathological feature: subepithelial bullae with significant infiltration of neutrophils. Some patients also presented additional SLE-related features in the histopathology, including dyskeratotic cells, liquefactive degeneration of the basement membrane, thickening of the epidermal basement membrane, and mucin deposition in the dermis.

2.3. Immunofluorescence characteristics

Patients underwent direct immunofluorescence testing for 5 markers, as well as indirect immunofluorescence using IgG and salt separation. Figure 3 shows the direct immunofluorescence (DIF) and salt-separated indirect immunofluorescence (SSS) images for patient number 12.

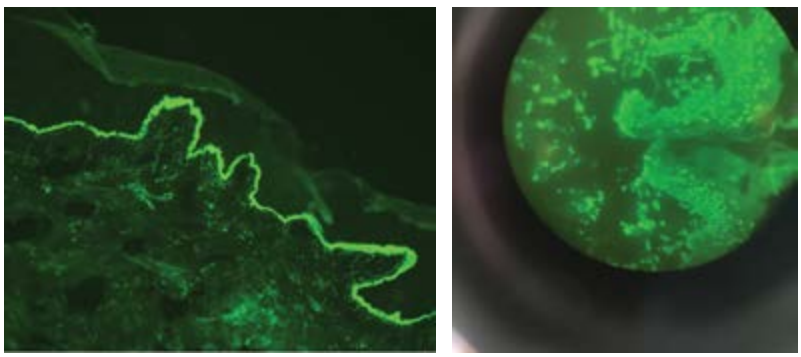

Figure 3. Immunofluorescence images for patient number 12: Direct immunofluorescence (DIF) shows positive IgG staining in a linear pattern along the basement membrane. Indirect salt separation immunofluorescence (SSS) reveals positive IgG in the nuclei of squamous epithelial cells and in a linear pattern at the base of the bullae

78.6% of patients had direct immunofluorescence (DIF) showing IgG positivity in a linear pattern at the basement membrane and vascular walls, while 21.4% had DIF showing coarse granular IgG along the basement membrane. Additionally, 71.4% of patients had DIF positivity for at least one other marker (IgA, IgM, C3, and Fibrinogen). All patients (100%) demonstrated indirect immunofluorescence and salt-split skin showing IgG positivity in the cell nuclei and a linear pattern at the base of the blisters.

2.4. Treatment and Follow-Up

Patients with Bullous Systemic Lupus Erythematosus (BSLE) who had no kidney involvement and no contraindications to dapson (with normal G6PD tests) received systemic treatment with dapson monotherapy, which led to a rapid response in controlling the blister lesions within 48 - 72 hours. For patients with concomitant kidney involvement or contraindications to dapson, systemic corticosteroids and immunosuppressive agents were added to the treatment regimen. After three months of follow-up, none of the patients experienced a recurrence of blister lesions. Below is an image of patient number 12 at the time of discharge, five days after starting dapson treatment.

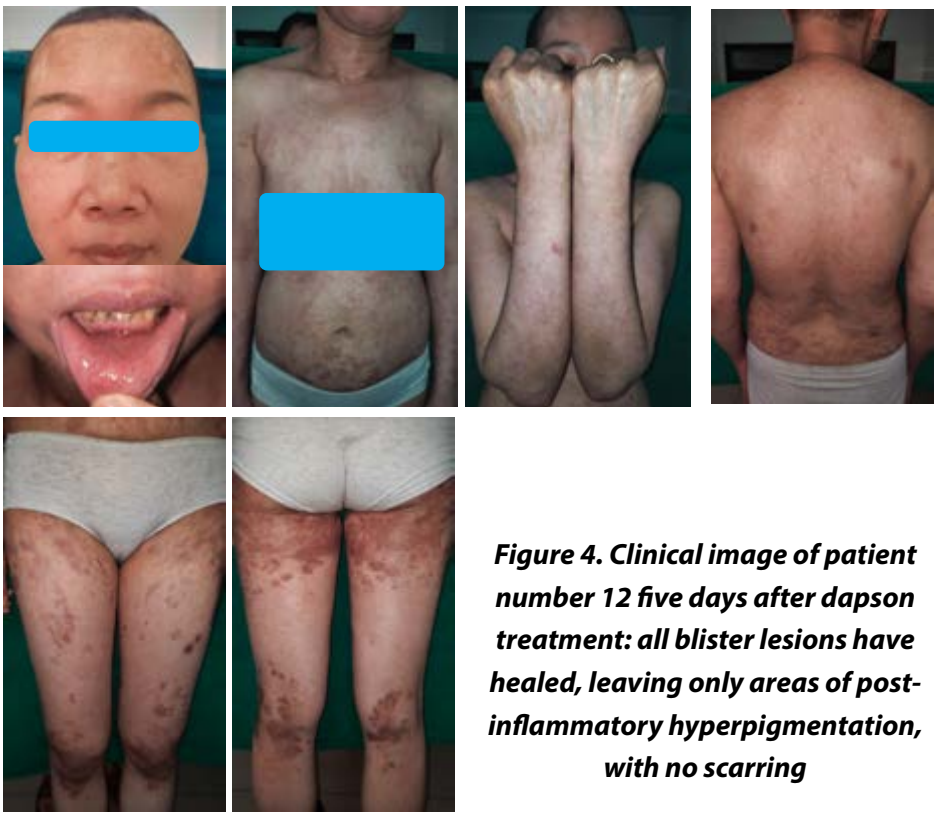

Figure 4. Clinical image of patient number 12 five days after dapson treatment: all blister lesions have healed, leaving only areas of post-inflammatory hyperpigmentation, with no scarring

3. DISCUSSION

In this study, 50% of BSLE patients were young women aged 20 - 40, consistent with other research[1,10]. The characteristics of age and gender in BSLE show no significant difference from SLE. Notably, 35.7% of BSLE patients presented with blister lesions without a prior diagnosis of SLE, complicating initial diagnostic orientation. Blisters were commonly located on the face, lip

margins, neck, trunk, and upper extremities, with less frequent occurrence on the lower extremities. There was no clear preference for areas exposed to sunlight. In addition to blister lesions, 71.4% of patients exhibited urticarial papules, followed by oral mucosal erosions in 64.3%. After treatment, 100% of patients had healed lesions, leaving only areas of post-inflammatory hyperpigmentation, with no milia or scarring. This characteristic helps distinguish BSLE from epidermolysis bullosa acquisita (EBA). Furthermore, 50% of patients in this study had accompanying nephritis, similar to findings in other studies[1].

Histologically, BSLE is characterized by subepithelial blisters with a predominant neutrophilic infiltrate in the blisters and superficial dermis. This may cause confusion with herpes dermatitis. Mucin deposition in the dermis and histological features of SLE help differentiate it more effectively from herpes dermatitis. In direct immunofluorescence, 70 - 80% of patients showed a linear IgG positivity at the junction, while the remaining exhibited granular deposition. Notably, there may be simultaneous positivity for IgM, IgA, C3, or Fibronogen. This characteristic can be confused with bullous pemphigoid (BP) or EBA. Regarding salt-split skin technique, BSLE, similar to EBA, exhibits antibody deposition at the base of the blister (u-serrated pattern), in contrast to BP, which shows deposition at the roof of the blister (n-serrated pattern). ELISA may detect antibodies against type VII collagen in type 1 BSLE (70%) or antibodies against BP230, BP180, laminin 5,6 in type 3 BSLE[1].

For the diagnosis of BSLE, the criteria established by Camisa and Shrama in 1983, modified in 1988[10,11], include five criteria: (1) satisfying ACR diagnostic criteria for SLE; (2) acute onset of blistering lesions; (3) histology showing subepithelial blisters primarily infiltrated by neutrophils; (4) direct immunofluorescence showing linear IgG deposition at the basement membrane, potentially accompanied by IgM, IgA; (5) indirect salt-split immunofluorescence showing IgG positivity at the base of the blister or ELISA detecting antibodies against type VII collagen.

The first-line treatment for BSLE is dapson at an initial dose of 50 - 100 mg/day, which usually leads to a rapid response within 24 - 48 hours[1,3]. This is similar to herpes dermatitis. Pre-treatment G6PD testing is necessary to prevent potential hemolytic side effects. Dapson may be continued for up to one year to minimize the risk of relapse[12,13]. If dapson is contraindicated or if there are organ involvement, alternative treatments include corticosteroids and immunosuppressive agents (azathioprine, mycophenolate mofetil, methotrexate)[1,6]. Recently, the biological agent Rituximab, a monoclonal antibody against CD20, has shown efficacy in some refractory BSLE cases resistant to dapson, corticosteroids, and other immunosuppressive therapies[14].

4. CONCLUSIONS

Bullous systemic lupus erythematosus (BSLE) is a rare subepithelial blistering condition with an autoimmune mechanism. Diagnosis of BSLE requires a combination of clinical assessment, histopathology, and immunofluorescence to differentiate it from other blistering diseases. The first-line treatment for BSLE is dapson, while cases with organ involvement require corticosteroids and other immunosuppressive medications, with careful monitoring for drug side effects. Managing SLE remains a top priority.

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