

Bullous systemic lupus erythematosus in females

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Abstract: Bullous systemic lupus erythematosus (BSLE) is a rare blistering presentation of systemic lupus erythematosus, typically affecting women with the highest incidence in those of African descent. The key pathogenic insult includes the formation of autoantibodies against type VII collagen, which weaken the basement membrane zone and lead to the formation of subepidermal blisters. The acute vesiculobullous eruptions in BSLE generally tend to affect photo-distributed areas, although they can arise unrelated to sun exposure (eg, mucous membranes, axillae). The bullae can arise from erythematous macules, inflammatory plaques, or previously normal skin. Their appearance can range from small, grouped vesicles reminiscent of lesions in dermatitis herpetiformis to large, tense blisters, similar to bullous pemphigoid. Internal organ involvement occurs in up to 90% of those affected. This mostly includes lupus nephritis (classes III–V, lifetime prevalence of up to 90%), arthralgias/arthritis, and cytopenias, while serositis and neuropsychiatric involvement are rare. First-line management with dapsone should be considered in mild disease with stable underlying systemic lupus erythematosus. As discussed in this review, the off-label use of rituximab (an anti-CD20 B-cell depleting agent) has been shown to be safe and effective in several refractory cases of BSLE unresponsive to dapsone, glucocorticoids, or steroid-sparing immunosuppressants.

Keywords: Bullous lupus, bullous systemic lupus erythematosus, type VII collagen, vesiculobullous skin disease

Introduction

Bullous systemic lupus erythematosus (BSLE) is a rare form of systemic lupus erythematosus (SLE) that typically manifests as an acute blistering eruption. There are various proposed criteria for BSLE diagnosis with common features including (1) features or a diagnosis of SLE based on the American College of Rheumatology criteria; (2) an acutely acquired vesiculobullous rash; (3) histopathologic evidence of a subepidermal blister and a dermal infiltrate consisting mostly of neutrophils; (4) direct immunofluorescence (DIF) demonstrating deposition of IgG, IgM, or IgA at the basement membrane zone (BMZ); (5) evidence of antibodies to type VII collagen; and (6) exclusion of other blistering disorders.^{1,2}

Epidemiology

Due to the rarity of this disorder, the exact prevalence of BSLE is unknown. Large cohort studies of SLE and cutaneous lupus erythematosus patients have shown a range of 0.19–0.41% of patients develop features of BSLE.^{3,4} Similar to the epidemiology of SLE, women are more frequently affected than men, with the highest

incidence in those of African descent in the second to fourth decades of life. However, it can present in all ages, races, and genders.

Etiology and pathogenesis

BSLE is a rare manifestation of SLE that typically presents in patients with an existing SLE diagnosis, although reports of BSLE in association with new-onset SLE have been reported.⁵ BSLE results from autoantibodies to type VII collagen located at the BMZ.² Type VII collagen plays a key role in connecting the dermis to the epidermis by acting as an anchoring fibril and cross-linking the lamina densa and dermal matrix.² Thus, the autoantibodies against type VII collagen weaken the basement membrane-dermal adhesion, leading to the appearance of subepidermal blisters.⁶ These autoantibodies specifically target the type VII collagen noncollagenous domains types 1 and 2 (NC1 and NC2) found in the BMZ.² Other autoantibodies that

What is known about this subject in regard to women and their families?

- Bullous systemic lupus erythematosus is a rare blistering presentation of systemic lupus erythematosus, typically affecting women with the highest incidence in those of African descent.
- The key pathogenic insult includes the formation of autoantibodies against type VII collagen, which weaken the basement membrane zone and lead to the formation of subepidermal blisters.
- First-line management with dapsone should be considered in mild disease with stable underlying systemic lupus erythematosus.

What is new from this article as messages for women and their families?

- The off-label use of rituximab (an anti-CD20 B-cell depleting agent) has been shown to be safe and effective in several refractory cases of bullous systemic lupus erythematosus unresponsive to dapsone, glucocorticoids, or steroid-sparing immunosuppressants.

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may play a role in the development of BSLE include bullous pemphigoid (BP) 180, BP 230, laminin 5, and laminin 6.⁷ It has been postulated that epitope spreading accounts for the antibody targets that exist in BSLE beyond type VII collagen.² The main autoimmune insult against type VII collagen could expose otherwise hidden antigens, leading to the increased number of autoantibodies found to be associated with BSLE.²

It is likely that immunoglobulin deposition causes the lamina densa portion of the basement membrane to separate from the upper dermis, resulting in bullae formation.² Type VII collagen autoantibodies may block or weaken the anchoring fibril connection to the lamina densa and anchoring plaques by interfering with extracellular matrix ligands, causing ineffective adhesion of the dermis to the lamina densa.² Antibodies present near the NC2 region may interfere with the antiparallel dimer alignment of type VII collagen, disrupting adherence to the dermis.² In vitro studies have also shown that type VII collagen autoantibodies can activate complement leading to the formation of complement-dependent peptides that induce neutrophil-dependent proteolysis at the BMZ.²

Clinical manifestations

Cutaneous findings

The clinical presentation of BSLE consists of an acute onset generalized vesiculobullous eruption in patients who meet criteria for SLE (Fig. 1).² Lesions can occur anywhere, although a predilection exists for the face, neck, upper torso, supraclavicular area, axillae, proximal extremities, and mucous membranes.^{1,2} Sun-exposed areas are more likely to be affected, although cases unrelated to photosensitivity have occurred.² Bullae tend to evolve from erythematous macules or inflammatory plaques though they can arise in previously clinically normal skin.² Bullae can vary from small clusters of vesicles resembling dermatitis herpetiformis (DH) to large, tense blisters similar to lesions of BP.² Pruritus may occur though patients often report a burning sensation associated with lesions.¹ The bullae tend to progress to erosions and heal without scarring most commonly, although dyspigmentation is typical.² Mechanobullous lesions and healing with scarring and milia, features of epidermolysis bullosa acquisita (EBA), are not usually found in BSLE.^{1,2} The primary lesions associated with SLE and discoid lupus are rarely seen with BSLE.²

Laboratory findings

As BSLE occurs in the context of SLE, the antinuclear antibodies will often be positive. Other autoantibodies that may be detected include anti-double stranded DNA, anti-Smith, anti-Sjögren's-syndrome-related antigen A, anti-Sjögren's-syndrome-related antigen B, and anticardiolipin. Other laboratory findings that may be seen in BSLE due to underlying SLE include anemia, leukopenia, thrombocytopenia, low levels of complement (eg, C3, C4, CH50), positive protein or cellular

casts in urine, and increased erythrocyte sedimentation rate. Historically, positive or negative indirect immunofluorescence for circulating BMZ antibodies against type VII collagen was proposed in the diagnostic criteria for BSLE created by Camisa and Sharma⁸ in 1983 and later revised in 1986.⁹ More recently, an enzyme-linked immunoassay has been used to detect autoantibodies against the NC1 and NC2 of type VII collagen.¹⁰ Anti-BP180, -BP230, and -laminin 5 or 6 may also be detected.²

Systemic involvement

Patients with BSLE can present with extracutaneous manifestations involving various organ systems. Patients with BSLE have concomitant internal organ involvement in 69–90% of reported cases.¹¹ Typically, extracutaneous findings are simultaneously present at the time of the diagnosis of BSLE, but additional findings may develop after the disease has been identified. The most common findings are arthralgias, arthritis, cytopenias, and lupus nephritis, with serositis and neuropsychiatric lupus described in only a few cases.^{3,11,12}

Renal involvement occurs concurrently in approximately 50% of patients, and up to 90% of patients with BSLE develop renal disease in their lifetime.^{3,11} Patients present with hematuria and proteinuria, generally attributed to lupus nephritis class III,^{11,13} class IV,^{11,14} or class V,^{15,16} according to the International Society of Nephrology/Renal Pathology Society classification. Granular deposition of IgG, IgM, IgA, C3, and C1q has been described on DIF of renal biopsies, unlike in the skin where both granular and linear patterns have been described.^{2,8,14,15}

The hematological system is another common site of involvement. Forty percent to 90% of patients experience either anemia or leukopenia, or the combination of the two, alongside BSLE.¹¹ While these findings may be due to BSLE, these abnormalities may be a result of the immunosuppressive therapies utilized for the treatment of BSLE/SLE.³

Patients also often demonstrate an increase in SLE activity (as evaluated with systemic lupus erythematosus disease activity index 2000), high antinuclear antibodies titers, elevated erythrocyte sedimentation rate, and low C3 levels in tandem with the development of BSLE.^{3,8,11,12,15,17}

Histopathology

Histologic findings in BSLE are classically described as similar to those seen in DH.² However, mucin deposits in the reticular dermis are a distinguishing feature of BSLE.¹ Bullae show separation of the epidermis from the dermis at the basal membrane with the overlying epidermis usually remaining intact.² The blister cavity is often full of fibrin and neutrophils.¹ There is also dermal edema and a dense inflammatory infiltrate of the upper dermis concentrated in the papillary tip consisting of predominantly neutrophils, although some monocytes and eosinophils are also typically present (Fig. 2).² Features of necrotizing vasculitis may also be found.² Many characteristic features of other types of cutaneous lupus erythematosus, such as basal keratinocyte vacuolization, interface dermatitis, BMZ thickening, and epidermal atrophy, are generally not found in the lesions associated with BSLE.¹

DIF staining of perilesional and unaffected skin shows the deposition of autoantibodies along the BMZ (Fig. 3). The majority of immunoglobulins are IgG, but other isotypes such as IgA and IgM can be found.² Complement components are often found in BSLE lesions.² IgG subtyping can help differentiate BSLE from EBA with overlapping features as EBA is primarily characterized by IgG1 and IgG4 subclasses while BSLE autoantibodies seem to predominantly be IgG2 and IgG3.^{18–20}

Some authors believe BSLE is a hybrid term used to describe various vesiculobullous cutaneous pathologies with distinct histologic patterns observed in the context of SLE. Ting et al.²¹ described 3 distinct histologic patterns observed: DH-like vesiculobullous lupus erythematosus (LE) consisting of neutrophilic



Fig. 1. Tense bullae typical of BSLE on a 15-y-old female patient (Courtesy of Dr. Julia Rood, MD, PhD). BSLE, bullous systemic lupus erythematosus.

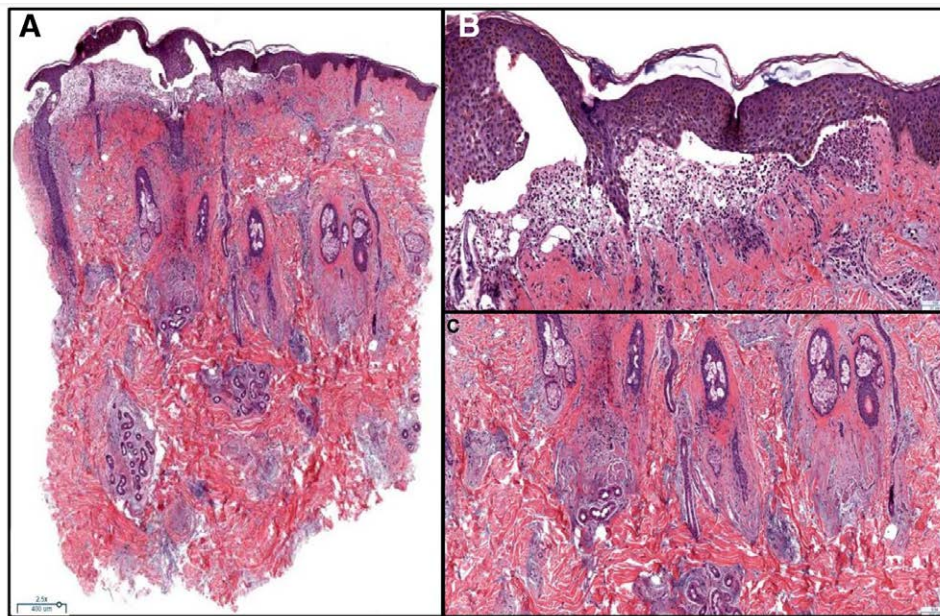


Fig. 2. Routine histology (hematoxylin and eosin) shows a subepidermal blister, superficial and deep perivascular and periadnexal inflammation, with intradermal mucin deposition at scanning power (A). The bullae and papillary dermis show a neutrophilic infiltrate with associated cytotlastic debris. Occasional civatte bodies and melanophages are seen (B). The deep periadnexal inflammation is lymphocytic, with scattered neutrophils. Deep dermal mucin is seen interstitially, as well as periadnexally around eccrine coils (C).

microabscesses in the dermal papillae along with granular deposition of IgA or IgG at the BMZ, EBA-like vesiculobullous LE with antibodies to type VII collagen, which bind to a dermal epitope on sodium chloride-split skin, and BP-like vesiculobullous LE with linear deposition of IgG and C3 at the BMZ. Table 1 summarizes the features of these histologic subtypes along with clinical attributes that can help distinguish these BSLE patterns from the mimicking autoimmune blistering condition.

Immunologic pathways

The exact immunologic pathways involved in the production of the autoantibodies that cause BSLE have not been completely elucidated. Multiple reports of rituximab, a chimeric monoclonal antibody that targets CD20, effectively treating BSLE indicate that CD20+ cells likely play a role in the pathogenesis of BSLE.^{13,15,22} This would implicate a role for immature, naïve, and memory B cells in the production of the autoantibodies associated with BSLE.

Differential diagnoses

Histologically, BSLE is characterized by separation at the BMZ, with IgG, IgM, or IgA deposition on the dermal side of BMZ-split skin, and a neutrophilic infiltrate in the superficial dermis. NC1 and NC2 autoantibodies against collagen VII represent the serologic marker of BSLE on enzyme-linked immunoassay. Clinically, BSLE is notable for often having a rapid response to dapsone therapy and usually exhibiting a short course with resolution within a year of diagnosis. BSLE can have varying manifestations through mimicking several autoimmune blistering conditions, especially the DH-like and EBA-like phenotypes (Table 1). The main differentiating clue for the diagnosis of BSLE is the presence of underlying SLE.

Management

Currently, dapsone is considered the first-line agent for mild BSLE with up to 90% efficacy,¹¹ with a rapid response within

days of initiation of therapy.²³ Dapsone is typically started at 50 mg per day and is increased by 25 mg each week after close lab monitoring, up to the maximum dose of 75 mg twice daily as tolerated (Fig. 4). Side effects include hemolytic anemia, which is expected, and a 2 g/dL drop in hemoglobin down to 10 g/dL is tolerated. Other potential side effects include methemoglobinemia, peripheral neuropathy, hepatotoxicity, pancreatitis, agranulocytosis/pancytopenia, and hypersensitivity syndromes.^{11,24} Patients may require steroid therapy for their BSLE if it is severe or if the underlying systemic SLE is active.

BSLE is well-known for its B-cell-mediated antibody production against collagen type VII. As with other immunobullous diseases, the use of anti-CD20 monoclonal antibodies has been safe and effective.²⁵ Initiation/augmentation of immunosuppressants (with or without dapsone therapy) due to systemic manifestations of SLE may result in the concurrent improvement of bullous lesions in BSLE.²⁶ Most patients respond to systemic glucocorticoids. If steroids (eg, prednisone) are to be used, it would be prudent to combine them with steroid-sparing agents, as is common with other immunobullous diseases (Fig. 4).

Since 1997, rituximab has been approved by the Food and Drug Administration, first for the treatment of low-grade or follicular non-Hodgkin lymphoma, and later for chronic lymphocytic leukemia, rheumatoid arthritis (RA), granulomatosis with polyangiitis, microscopic polyangiitis, Waldenström's macroglobulinemia, and pemphigus vulgaris.^{27–30} Similarly, the off-label use of rituximab in SLE, BSLE and other B-cell mediated conditions has a long history.^{31,32} Rituximab is notable for its activity against the CD20-bearing pre-B and B cells (including immature, naïve, and memory cells); however, it is ineffective against terminally differentiated plasma cells. Following the administration of rituximab, B cells are depleted immediately, while the half-life of autoantibodies is about 3 weeks. Therefore, it can take up to 3–4 months for the autoantibodies to decline enough to see the clinical response. Relapses can occur after the repletion of autoreactive B cells, frequently 12–18 months after treatment, which may require another course of rituximab. Serious adverse events are rare, the most common being bacterial sepsis. Progressive multifocal leukoencephalopathy (PML)

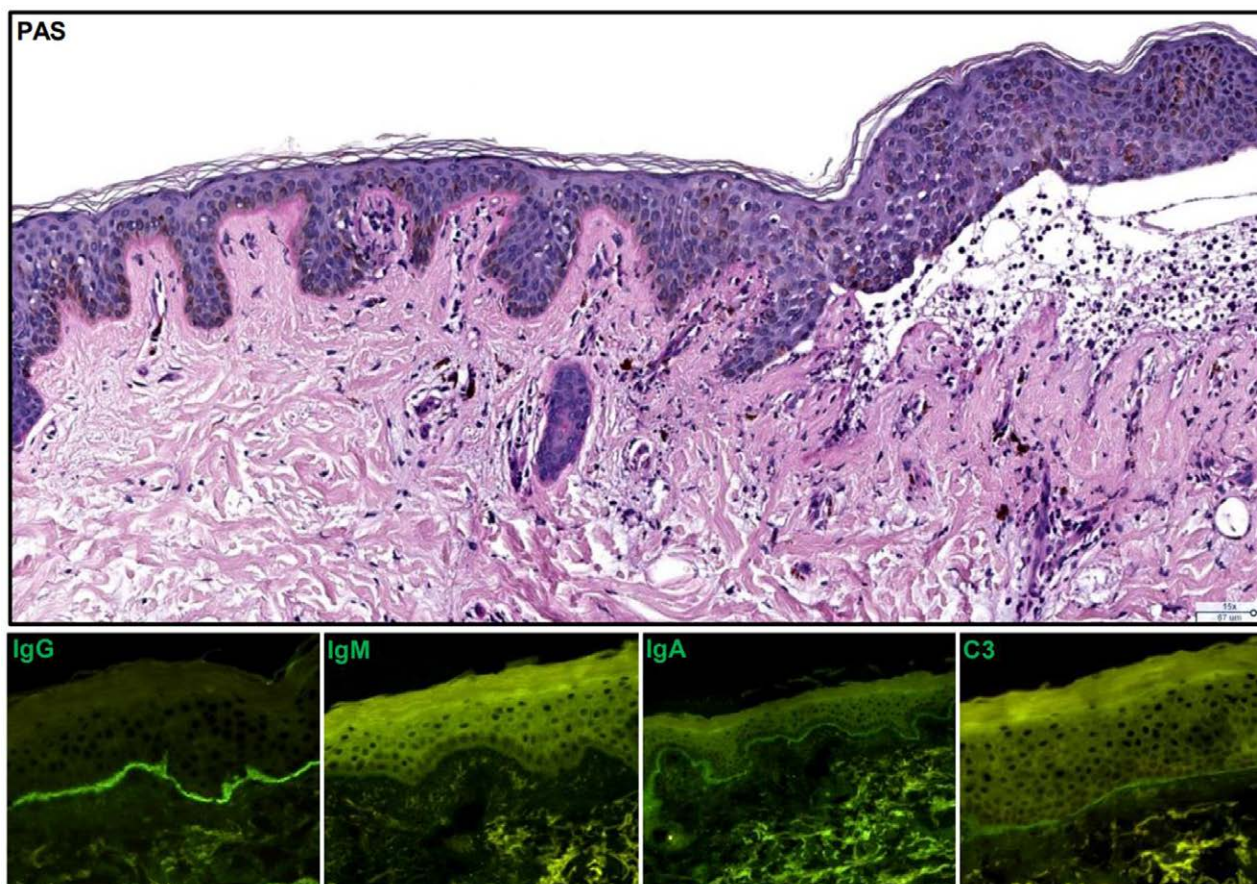


Fig. 3. PAS staining shows basement membrane thickening in skin that is adjacent to bullae. DIF demonstrates deposition of IgG, IgA, and C3 at the BMZ. BMZ, basement membrane zone; DIF, direct immunofluorescence; PAS, periodic acid-Schiff.

is a serious, although very rare, complication seen primarily in cancer patients, and rarely in SLE.³³ However, no clinically suspected or confirmed cases of PML have been reported among pemphigus patients.³³ The median time interval from the last dose of rituximab to PML diagnosis is about 5.5 months.³⁴

In 2011, we reported the first use of rituximab for the management of refractory BSLE with rapid clearance of lesions in a 61-year-old woman of African American origin who was earlier diagnosed with the SLE/Sjögren overlap syndrome.²² Prior to treatment with rituximab, she had remained unresponsive to hydroxychloroquine (400 mg/d), azathioprine, and mycophenolate mofetil (up to 2,000 mg/d), while dapsone had to be stopped due to elevated liver enzymes.²² A few years later, we reported another successful use of rituximab in a 42-year-old

woman with BSLE unresponsive to dapsone, hydroxychloroquine, azathioprine, methotrexate, and prednisone at doses of up to 120 mg per day, with the lesions clearing 2 weeks after rituximab administration.³⁵ In both cases, rituximab was administered via 2 infusions of 1000 mg each given 2 weeks apart per the RA dosing regimen.³⁵ Alternatively, rituximab can be administered according to the lymphoma dosing regimen with weekly infusions of 375 mg/m² over a 4-week period. However, the choice of dosing regimen is often dictated by insurance (Fig. 4). Repeated use of rituximab over a 5-year period was safe and effective for BSLE flares in an 18-year-old African American woman with childhood onset of BSLE extending into her late teens and early adulthood.³⁶ In this case, rituximab given via the RA dosing regimen was the only agent to consistently result

Table 1
Histologic subtypes of BSLE

Histologic subtypes	Features
DH-like vesiculobullous LE	Neutrophilic microabscesses in the dermal papillae Dense granular deposition of IgA or IgG at the BMZ Mucin deposits in the reticular dermis more commonly found than in true DH Concurrent SLE diagnosis Fails to improve with a gluten-free diet, unlike true DH
EBA-like vesiculobullous LE	Antibodies to type VII collagen which bind to a dermal epitope on sodium chloride-split skin Autoantibodies are predominantly IgG2 and IgG3 subclasses, unlike in true EBA where they are typically IgG1 and IgG4 Concurrent SLE diagnosis
BP-like vesiculobullous LE	Linear deposition of IgG and C3 at the BMZ with IgG largely below the basal lamina on immunoelectron microscopy Concurrent SLE diagnosis

BMZ, basement membrane zone; BP, bullous pemphigoid; BSLE, bullous systemic lupus erythematosus; DH, dermatitis herpetiformis; EBA, epidermolysis bullosa acquisita; LE, lupus erythematosus; SLE, systemic lupus erythematosus.

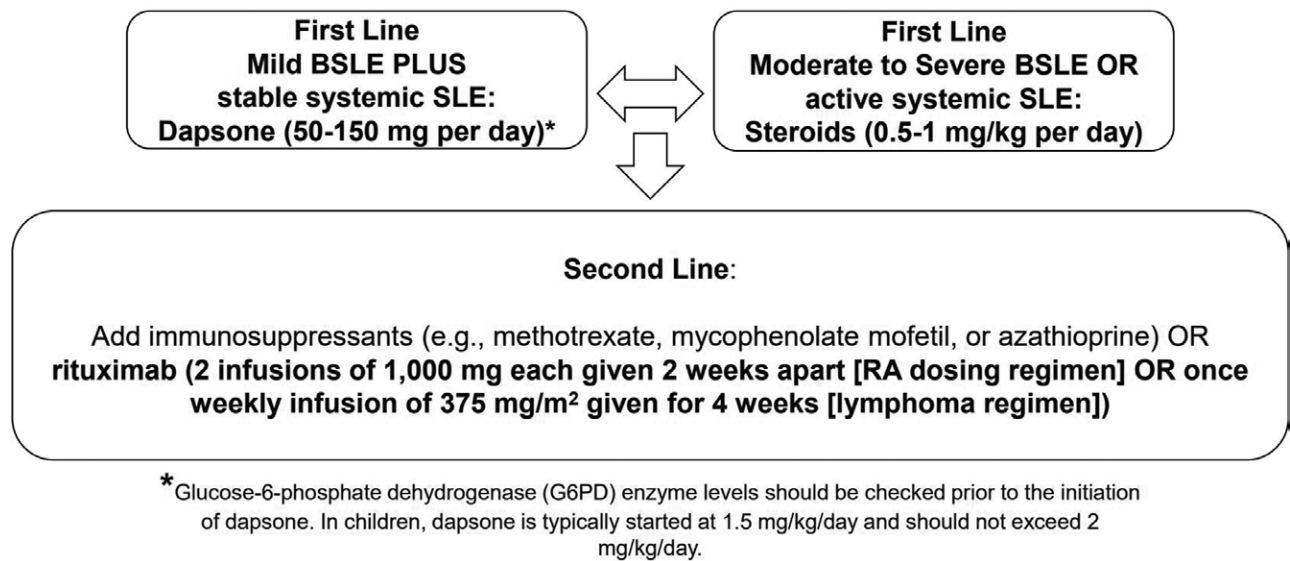


Fig. 4. Proposed therapeutic ladder for BSLE. BSLE, bullous systemic lupus erythematosus; G6PD, glucose-6-phosphate dehydrogenase; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

in the resolution of both cutaneous and systemic disease during multiple episodes of BSLE.³⁶ Presence of active underlying SLE should be considered in the management of individuals with BSLE (Fig. 4).

Less frequently, anakinra (an interleukin-1 receptor antagonist) and intravenous immunoglobulin have been reported in the management of refractory BSLE.¹¹ However, it has been hypothesized that the use of intravenous immunoglobulin might result in a paradoxical “compensatory” surge of B cell-mediated antibody production and subsequent BSLE exacerbation, unless the B cells are blocked with immunosuppressants or steroids.

Conclusions

BSLE is a rare sequela of SLE that typically presents as an acute blistering eruption primarily in women. It is characterized by clinical and histopathologic features similar to EBA and DH with autoantibodies to type VII collagen being characteristic. Biopsy should be obtained for an accurate diagnosis and will show subepidermal blisters, a neutrophil-predominant dermal infiltrate, and autoantibody deposition at the BMZ. Patients should also be carefully evaluated for concomitant internal organ involvement. Dapsone is typically initiated in patients with milder disease, while patients with more severe disease or those not responding to dapsone can be treated with steroids (with or without immunosuppressives) or rituximab.

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Author contributions

GS, MA, JD, and MLH participated in the writing of the article. VPW participated in the writing of the article and critically revised it. All authors approve of the final version.

Conflicts of interest

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