




Refractory Bullous Systemic Lupus Erythematosus Successfully Treated with Rituximab: A Case Report and Literature Review

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Abstract: Bullous systemic lupus erythematosus (BSLE) is a rare blistering skin manifestation of systemic lupus erythematosus (SLE). Dapsone is reported to be helpful in mild-to-moderate BSLE cases; however, its use may be limited or prohibited due to particular complications such as drug hypersensitivity, dose-dependent hemolytic anemia, and other significant hematologic abnormalities. Rituximab, an anti-CD20 monoclonal antibody, has been reported with off-label use in BSLE patients, but data are still limited. Hence, our objective is to explore the efficacy of rituximab among these patients. Herein, we report a 21-year-old Thai woman presented with blistering eruption on the oral cavity, scalp, trunk, and extremities for 1 month. The investigations revealed a positive direct Coomb's test, an elevated erythrocyte sedimentation rate (ESR), and a positive antinuclear antibody (ANA). Skin biopsy showed focal interface dermatitis. Direct immunofluorescence (DIF) illustrated mixed linear and granular deposition of immunoglobulin (Ig)G, IgM, IgA, and C3 along the dermo-epidermal junction (DEJ). Enzyme-linked immunosorbent assay (ELISA) showed circulating antibodies to type VII collagen. She was diagnosed with severe BSLE and autoimmune hemolytic anemia (AIHA) refractory to several oral immunosuppressants but was successfully treated with rituximab. The authors also performed a review of the literature on prior BSLE cases managed with rituximab.

Keywords: anti-CD20 monoclonal antibody, autoimmune bullous diseases, systemic lupus erythematosus, bullous systemic lupus erythematosus, subepidermal blistering eruption

Introduction

BSLE is an uncommon autoimmune subepidermal blistering eruption that can occur in patients with SLE. It typically affects young women in the second to fourth decades of life.¹⁻⁴ Although 59% to 85% of SLE patients develop cutaneous manifestations, BSLE affects less than 5% of lupus patients^{1,5-8} and approximately 2-3% of all subepidermal autoimmune bullous skin diseases.⁹ A large cohort of studies showed that 0.19-0.41% of SLE and cutaneous lupus erythematosus patients develop BSLE.^{8,10} The highest incidence is in those of African descent. However, it can present in all ages, races, and genders.¹¹

BSLE typically presents with a subepidermal tense vesiculobullous eruption that heals without scarring. It affects mainly the trunk, upper extremities, neck, face, and vermillion borders but can also occur anywhere.¹ Some cases of BSLE are associated with increased SLE activity, particularly lupus nephritis.^{1,12-14} BSLE is characterized histologically by a subepidermal blister, with a predominantly neutrophilic dermal infiltrate. Immunofluorescence examination shows deposition of IgG, IgA, IgM, and complement (C) along the basement membrane zone (BMZ).^{8,15} The presence of circulating antibody on the dermal side of the BMZ can be presented. A major target antigen in patients with BSLE is the anchoring fibril component type VII collagen in the dermis.^{8,16} Treatment with dapsone, glucocorticoids, antimalarial agents, and other immunosuppressives has shown variable efficacy. Off-label use of rituximab has led to successful outcomes in refractory BSLE cases.^{2,4,17,18} Rituximab depletes mature B-cells that are CD20 positive and therefore likely to reduce the quantity of circulating anti-type VII collagen antibodies, which are responsible for bullae formation in

BSLE.¹ However, there are still limited studies regarding the use of rituximab in severe BSLE. In addition, the duration of remission, rate of relapse, and whether repeated infusion is necessary remains unclear. We, herein, report a 21-year-old Thai woman with severe BSLE successfully treated with rituximab and include a review of the literature on prior BSLE cases managed with rituximab. The search for English-language publications was conducted using the PubMed database. The specific search term was “bullous systemic lupus erythematosus [text word]” (no exclusions were utilized); thereafter, a manual search of case reports/series and review articles reporting rituximab treatment as well as each article’s references was undertaken to ensure a more complete sample of existing literature.

Case Report

A 21-year-old Thai female diagnosed with severe BSLE and autoimmune hemolytic anemia (AIHA) presented with blistering eruption on the lips, hard palate, scalp, trunk, upper and lower extremities with desquamation of the palms and soles for 1 month. She also had non-scarring alopecia and arthralgia. Physical examination revealed multiple tense vesicles on lips, hard palate, and scalp; multiple tense bullae on erythematous base at trunk and extremities, accompanied with erythematous desquamated plaques on the palms and soles (Figure 1). Laboratory findings demonstrated hemolytic anemia with a positive direct Coomb’s test, an elevated ESR, and positive ANA with fine speckled (titer 1:320) and nucleolar (titer 1:80) pattern. A skin biopsy from left arm showed focal interface dermatitis. Direct immunofluorescence (DIF) illustrated mixed linear and granular deposition of IgG, IgA, and C3 as well as granular deposition of IgM along the dermo-epidermal junction, IgM deposition at superficial blood vessels, few cytotoid bodies of IgM and IgA, and perifollicular deposition of C3 (Figure 2). ELISA showed circulating antibodies to type VII collagen (>200 RU/mL). She was initially treated with dapsone (25–50 mg/day), prednisolone (30–40 mg/day), colchicine (0.6 mg/day), and clobetasol cream twice daily for 1 months. Then, hydroxychloroquine (200 mg/day) and azathioprine (50mg/day) were added. The treatment response was monitored for another 2 months. However, the cutaneous lesions persisted with multiple new tense bullae appearing on back, trunk, scalp, and extremities. Thereafter, the patient was administered with 1 g of pulse methylprednisolone for 3 days and 500 mg of intravenous cyclophosphamide (IVCY) every 2 weeks for 4 sessions. The combination treatment with IVCY and oral immunosuppressants was continued for 2 months. The dosage of oral prednisolone was increased to 60 mg/day, while dapsone was limited to 50 mg/day due to hematological concerns. Additionally, mycophenolate mofetil (1000 mg/day), cyclophosphamide (100 mg/day), and methotrexate (10 mg/week)

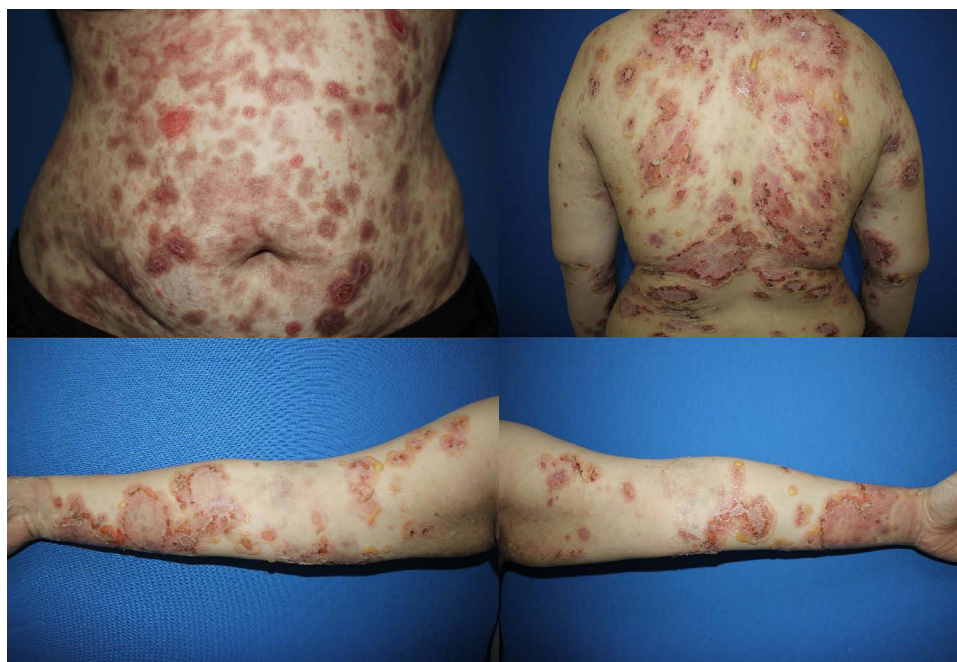


Figure 1 A 21-year-old female diagnosed with severe BSLE and autoimmune hemolytic anemia. Multiple tense bullae on erythematous base at trunk and extremities.

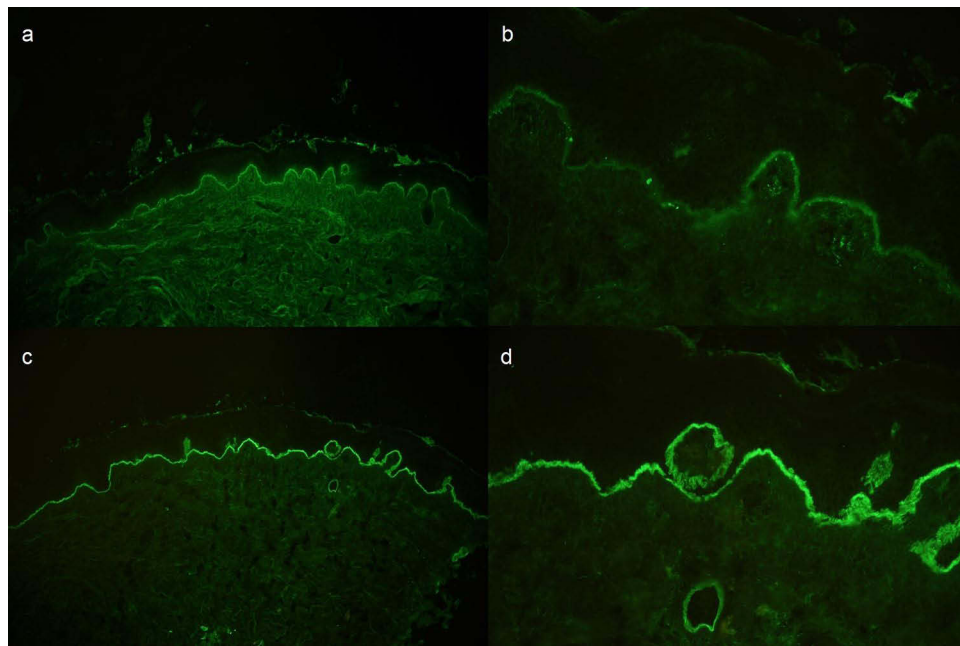


Figure 2 Direct immunofluorescence, (a) mixed linear and granular deposition of IgG along dermo-epidermal junction (DEJ), (b) Granular deposition of IgM along DEJ and superficial blood vessel, (c and d) mixed linear and granular deposition the along DEJ and perfollicular granular deposition of C3.

were added for 1 month. Nevertheless, the cutaneous disease remained refractory to the treatment. She finally received a rheumatoid arthritis protocol for rituximab consisting of two 1000 mg infusions 2 weeks apart. The patient responded well to rituximab, the oral lesions improved within 7 days after the first dose, and the skin lesions improved within 9 days after the second dose. Most of the lesions healed with post-inflammatory hyperpigmentation within 1 month, as shown in Figure 3. Prednisone was successfully tapered, and other immunosuppressants were decreased to minimal dose. Nevertheless, she developed a flare of BSLE at 6 months following the initial course of rituximab. She underwent

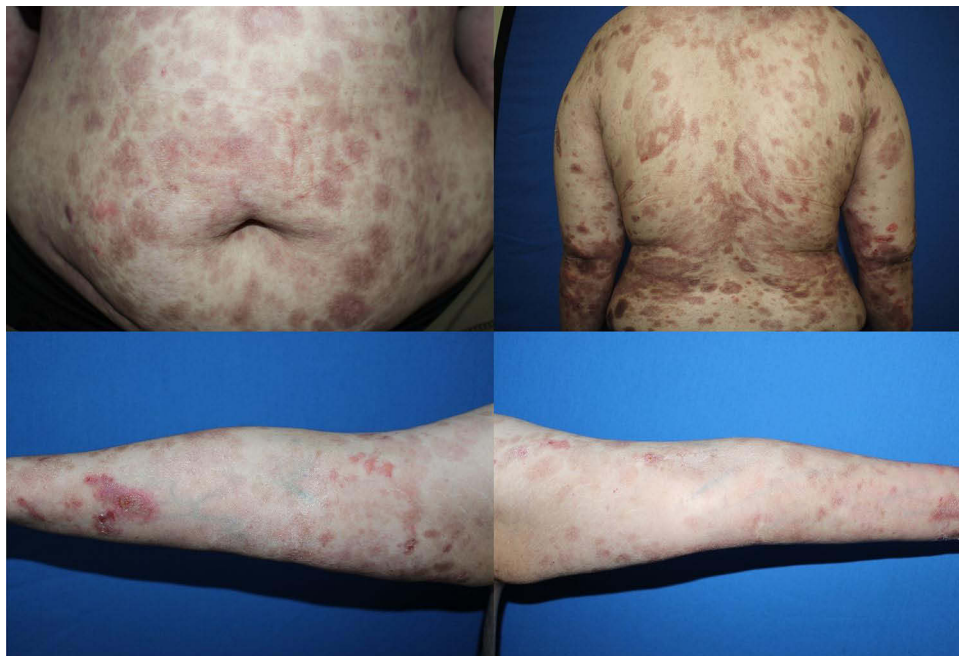


Figure 3 Improvement of BSLE after rituximab therapy. One month after 2 intravenous infusions of rituximab 1000 mg with a 2-week interval apart, most of the lesions healed with post-inflammatory hyperpigmentation.

another course of two infusions of rituximab 1000 mg administered 2 weeks apart and is currently in remission under minimal immunosuppressive therapy for 6 months.

Discussion

BSLE is a rare cutaneous manifestation of SLE, which is a LE-nonspecific vesiculobullous disease with an antibody targeting type VII collagen and histological evidence of neutrophilic dermatitis.^{1,19} The diagnostic criteria for BSLE were first described by Camisa and Sharma in 1983¹² and revised in 1988.¹⁴ These criteria included (1) a diagnosis of SLE based on the American College of Rheumatology (ACR) criteria; (2) the presence of vesicles and/or bullae; (3) the presence of histopathological features similar to those of dermatitis herpetiformis (DH); (4) DIF findings showing IgG, IgM, or IgA at the BMZ; and (5) IIF findings negative or positive for circulating autoantibodies against the BMZ. In 1995, Yell et al defined BSLE as “an acquired subepidermal blistering disease in a patient with SLE, with immune reactants at the BMZ on either DIF or IIF”. They subdivided BSLE into three classes based on the presence of antibodies to type VII collagen and location of the antibodies against the BMZ.^{20,21} In our case, the differential diagnoses include bullous pemphigoid, linear IgA bullous dermatosis, DH, and epidermolysis bullosa acquisita. She was diagnosed with SLE by fulfilling the EULAR/ACR criteria²² and had compatible clinical and immunopathological findings for BSLE. The patient was further classified as having type I BSLE due to the presence of circulating autoantibodies to type VII collagen, which is the most common subtype.

While systemic steroids and antimalarials are the standard treatments for the cutaneous manifestations of SLE, dapsone is the mainstay of treatment in BSLE, with a rapid clinical response.⁵ However, it is not uncommon for patients to be unresponsive to dapsone. Our patient was treated with dapsone in combination with several immunosuppressants for 3 months without clinical improvement. In addition, like this case the use of dapsone may be limited or prohibited in BSLE with significant hematologic abnormalities such as AIHA. Recently, rituximab, an anti-CD20 monoclonal antibody, has emerged as an effective therapy for treating a wide spectrum of diseases that include various rheumatic, gastrointestinal, and cutaneous diseases, and has shown promising results in BSLE cases refractory to dapsone, corticosteroids, or immunosuppressants.^{1,5} Rituximab depletes mature B-cells that are CD20 positive and therefore likely reduces the quantity of circulating anti-type VII collagen antibodies in the case of BSLE.

Rituximab was approved by the US Food and Drug Administration (FDA) for the treatment of malignancies, rheumatoid arthritis and later for pemphigus vulgaris.^{2,23} It has been used off label to treat BSLE cases that are resistant to dapsone, corticosteroids, and other immunosuppressants. However, there are limited case reports demonstrating rituximab treatment outcome and the time of treatment response in severe BSLE cases. In addition, long-term efficacy of rituximab is not known. Table 1 shows demographic data, clinical, laboratory, treatment, and outcome of existing severe BSLE cases treated with rituximab.

In 2011, Alsanafi et al reported a case of 61-year-old African American woman with overlapping SLE/Sjogren syndrome presented with refractory BSLE who was successfully treated with rituximab. The skin lesions improved within 10 days after the first dose and cleared by day 15 after the second dose. She remained free of recurrence of blistering lesions for 6 months.² In 2013, Anyanwu et al reported successful treatment of refractory BSLE in a 42-year-old woman who had bullous lupus lesions cleared for 2 years after receiving rituximab treatment.¹⁷ In 2019, Lowe et al reported an 18-year-old African woman with BSLE whose bullous eruption resolved after administering rituximab and was in remission under low-dose prednisolone (5mg) for a duration of 2 years.⁴ The most recent case report demonstrated a 39-year-old woman with severe BSLE who was successfully treated with low-dose rituximab at a dose of 500 mg 2 weeks apart (due to cost considerations). Skin lesions resolved completely after 3 months and remained stable at 1-year post-treatment.¹⁸ Similar to these previous reports, our case showed promising resolution of cutaneous lesions after rituximab treatment in severe BSLE that has limited response to dapsone, corticosteroid, antimalarial agent, and other immunosuppressants. However, the response to rituximab was relatively short and relapsed occurred after 6 months. Therefore, the existing evidence suggests a potential role for treatment of refractory BSLE with rituximab, but we also emphasize that its effectiveness may be short and patients may require repeated infusions.

Table 1 Demographic Data, Clinical, Laboratory Characteristics, Treatment, and Outcome of Severe BSLE Treated with Rituximab

No.	Age/Sex	Cutaneous Lesions	Extracuta-Neous Findings	Laboratory Investigations	Standard Treatments (Dosage)	Rituxima-b Treatment	Response	Relapse
Our case	21/Female	Tense bullae at lip, hard palate, scalp, trunk, and extremities	AIHA	ANA fine speckled 1:320, nucleolar 1:80 Complement: normal DCT 3+ ESR 36 mm/hour	Dapsone (50 mg/day) Colchicine (0.6 mg/day) Hydroxychloroquine (200 mg/day) Azathioprine (50 mg/day) Pulse methylprednisolone (1 gram for 3 days) IVCY (500 mg every 2 weeks for 4 sessions) Prednisolone (60 mg/day) Mycophenolate mofetil (1000 mg/d) Oral cyclophosphamide (100 mg/day) Methotrexate (10 mg/week)	2 IV infusions of rituximab 1000 mg with a 2-week interval	Mucocutaneous blister improved within 2 weeks of rituximab.	Flare of BSLE at 6 months
Alsanafi et al 2011 ²	61/Female	Tense blisters at arms and hands		ANA 1:640 Anti-RNP: positive, Anti-dsDNA: positive C3: low C4: low	Dapsone (N/A) Prednisolone (N/A) Azathioprine (N/A) Mycophenolate mofetil (2000 mg/day)	2 IV infusions of rituximab 1000 mg with a 2-week interval	Skin lesions cleared within 15 days of rituximab.	Free of recurrence after 6 months follow-up.
Anyanwu et al 2013 ¹⁷	42/Female	Tense bullae at trunk and buccal mucosa		ANA: positive Anti-dsDNA: positive Anti-Sm: positive IgM anticardiolipin: positive	Dapsone (N/A) Prednisone (120 mg/day) Hydroxychloroquine (N/A) Azathioprine (N/A) Methotrexate (N/A)	2 IV infusions of rituximab 1000 mg with a 2-week interval	The blistering ceased, and existing lesions healed after 2 weeks of receiving rituximab	Relapse at 2 years

(Continued)

Table 1 (Continued).

No.	Age/Sex	Cutaneous Lesions	Extracuta-Neous Findings	Laboratory Investigations	Standard Treatments (Dosage)	Rituxima-b Treatment	Response	Relapse
Lowe et al 2019 ⁴	18/Female	Tense, fluid-filled vesicles at cheeks, chin, postauricular area, vermilion border, oral mucosa, neck and shoulder	AIHA	ANA 1:640 DCT: positive Complement: low ERS: elevated	Prednisone (N/A) Hydroxychloroquine (N/A) Mycophenolate mofetil (N/A) IVIg (N/A)	2 IV infusions of rituximab 1000 mg with a 2-week interval	The bullous eruption resolved	Remission with minimal therapy for 2 years following
Akpabio and Otike-Odibi 2020 ¹⁸	39/Female	Bullous rashes at face, trunk and arms	Lupus nephritis (class I)	ANA speckled 1:5120 Anti-dsDNA 300 IU/mL ESR 48 mm/hour	Dapsone (50 mg/day) Prednisolone (20 mg/day) Hydroxychloroquine (200 mg/day) Mycophenolate mofetil (2000 mg/day)	2 IV infusions of rituximab 500 mg with a 2-week interval	Skin lesions resolved completely after 3 months with residual hyperpigmentation	Remained stable at 1 year post-treatment

Abbreviations: AIHA, autoimmune hemolytic anemia; ANA, anti-nuclear antibody; Anti-dsDNA, double-stranded deoxyribonucleic antibody; Anti-RNP, ribonucleoprotein antibody; Anti-Sm, anti-Smith antibody; BSLE, bullous systemic lupus erythematosus; C, complement; DCT, direct Coomb's test; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; IV, intravenous; IVCY, intravenous cyclophosphamide; IVIg, intravenous immunoglobulin; IU, international unit; mg, milligram; mL, milliliter; mm, millimeter; N/A, not available.

Conclusion

We report a case of severe BSLE refractory to low-dose of dapsone, antimalarial agent, corticosteroid, and several immunosuppressants that finally responded well to rituximab and emphasize the potential role of rituximab in the treatment of refractory BSLE through a review of the literature.

Ethics Approval and Consent to Participate

This article was performed in accordance with the principles of Declaration of Helsinki. Ethical review and approval were not required to publish the case details in accordance with local legislation and institutional requirements. Written informed consent was obtained from the patient for publication of this case report and any accompanying images as per our standard institutional rules.

Disclosure

The authors report no conflicts of interest in this work.

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