**Abstract.** – INTRODUCTION: Bullous systemic lupus erythematosus (BSLE) is a rare form of subcutaneous blistering lupus erythematosus (SLE). There is currently no effective treatment for BSLE. However, here, we present the first report of the successful treatment of refractory BSLE with belimumab in a 16-year-old girl.

**CASE PRESENTATION:** A 16-year-old girl with BSLE had undergone different treatment options, with no significant improvement. Since B-lymphocyte stimulator plays an important role in the pathophysiology of SLE, belimumab was administered and showed remarkable effects for the first time in this patient with both SLE and BSLE. The patient’s skin lesions improved steadily over the course of three weeks and completely disappeared in 30 days. In addition, no sign of recurrence of BSLE was observed over the 9-month follow-up period.

**CONCLUSIONS:** To our knowledge, this is the first report of the successful short-term therapy of refractory BSLE/SLE overlap syndrome with belimumab in a pediatric patient. Although the use of belimumab resulted in excellent

**Key Words:** Belimumab, Bullous systemic lupus erythematosus, Treatment, Case presentation.

**Abbreviations**

Anti-dsDNA: anti-double stranded deoxyribonucleic acid; ABSD: autoimmune bullous skin disease; BLyS: B-lymphocyte stimulator; Ig: immunoglobulin; MTX: methotrexate; HCQ: hydroxychloroquine; FDA: Food and Drug Administration; C3: complement 3; C4: complement 4 IVIG: intravenous gamma globulin; SLE-DAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000.

**Introduction**

Bullous systemic lupus erythematosus (BSLE) is a rare autoimmune blistering condition that occurs in patients with SLE\(^1\). The most common presentation is the rapid and widespread development of tense vesicles and bullae over erythematous macules or plaques. The prevalence of BSLE has been reported to be 0.41-0.6%\(^2\). BSLE is a rare, early clinical sign of SLE and there is a lack of large-scale randomized controlled trials and standardized treatment strategies for BSLE.

Although immune deposits, acute inflammation, and dermal basement membrane blistering suggest a complex immunological etiology for BSLE, the pathogenesis of BSLE remains unclear\(^3\). Separation within the dermal-epidermal junction, a neutrophilic infiltrate in the superficial dermis, immunoglobulin (Ig) G deposition at the dermal-epidermal junction, and antibody deposition on the dermal side of basement membrane zone-split skin are all classic histological and immunofluorescence features of BSLE.

Bulla formation may be caused by complement activation mediated by antibodies, and anti-collagen VII autoantibodies are typically used to diagnose BSLE\(^4\).

The treatment of BSLE is mainly empirical. Although dapsone is the first-line therapy for BSLE, it is a scarce medication in China because of a halt in production. Other immunosuppressants, such as corticosteroids, methotrexate (MTX), hydroxychloroquine (HCQ), azathioprine, and biologics, have been evaluated as treatment alternatives for BSLE\(^5\-7\).

Belimumab is the first B-lymphocyte stimulator (BLyS) inhibitor. It is a recombinant IgG2a monoclonal antibody (Benlysta, GSK, Brentford, UK) that binds to soluble BLyS with high affinity, blocking its function in B-cell-mediated immunity and autoimmune response. The United States Food and Drug Administration (FDA) recently approved belimumab for the treatment of childhood-onset SLE in children ≥ 5 years of age\(^8\).

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While belimumab may be a suitable alternative therapy for complications of SLE⁹,¹⁰, its efficacy in treating BSLE remains unclear. This study aimed to evaluate the response of a 16-year-old girl to belimumab therapy for refractory BSLE and to highlight the potential of BLyS inhibitor therapy in reducing inflammation in skin lesions. We demonstrated the potential role of belimumab in target therapy for refractory BSLE.

**Case Presentation**

A 16-year-old Chinese girl of Han nationality presented with a 1-month history of fever, vesicular bullous skin lesions, and mouth ulcers. She was diagnosed with SLE on June 21, 2021. For the next 20 days, she was administered oral corticosteroid (25 mg/day), HCQ (three tablets daily, 6.5 mg/kg/day daily), and intravenous gamma globulin (IVIG; 0.4 g/kg/day). However, with the continued low fever, the patient’s skin condition worsened.

The patient was admitted to our hospital on July 6, 2021, for further management after extensive vesicular skin lesions developed across her body, including a facial rash. A dermatological examination revealed tense clustered vesicles and blisters on her neck, torso, and extremities (Figure 1A). Nikolsky’s sign was negative. There was no joint swelling, alopecia, photosensitivity, or mucosal involvement. Her respiratory and cardiovascular systems appeared normal, and no overt flaws were discovered on general examination. The patient had no personal history of chronic diseases, infections, or drug use or relevant family history.

Laboratory investigations yielded the following findings: erythrocyte sedimentation rate, 29 mm/h (normal, 0-20 mm/h); hemoglobin, 100 g/L (normal, 115-150 g/L); antinuclear antibody 1, 1280 positive (granular pattern); anti-smooth muscle antibodies, positive; anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibody, 303.66 IU/ml (normal, 0-200 IU/ml); anti-nucleosome antibodies, 96.51 RU/ml (normal, 0-20 RU/ml); IgG, 19.4 g/L (normal 7.5-15.6 g/L); complement 3 (C3), 0.45 g/L (normal, 0.8-1.5 g/L); complement 4 (C4), 0.097 g/L (normal, 0.16-0.3 g/L); and 24 h urine protein quantification, 0.192 g. Her white blood cells, platelets were normal, while Coombs test, anti-cardiolipin IgG and IgM antibodies, human immunodeficiency virus, syphilis, hepatitis B, QuantiFERON-TB, and hepatitis C were all nega-

*Figure 1.* Changes in the patient’s bullous skin lesions before and after belimumab treatment. **A,** At the first visit, grouped tense vesicles and blisters on the neck. **B,** One week after the administration of belimumab, the patient’s neck showed slowly improvement in skin lesion. **C,** Three weeks after the administration of belimumab, the patient’s neck showed a significant improvement in bullous. **D,** No bullous skin lesions flare after 9-month of treatment with belimumab.
tive. Her Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) was 10.

A lesion located on the right side of her back was biopsied. Pathological examination revealed separation of the subepithelial vesicles and true epidermis, with dermal papillary layer edema and a large amount of inflammatory cell leaching (mainly neutrophils), and slightly dilated small vessels in the superficial layer of the dermis. Direct immunofluorescence revealed IgG, IgM, IgA, and C3 linear deposition in the basement membrane area (Figure 2A, 2B). Based on the clinical data and fulfillment of diagnostic criteria, the patient was diagnosed with BSLE3.

The patient was started on intravenous methylprednisolone (40-80 mg daily), HCQ 0.2 (twice daily), and cyclosporine 75 mg (twice daily) for 2 weeks, followed by a course of IVIG treatment. However, when the dose of the systemic steroids was lowered, more severe blisters emerged.

The patient’s skin lesions were severe, and upgradation of the biological agents was considered. Owing to unavailability of dapsone, the authors focused on rituximab and belimumab.

As previously stated, belimumab is the only biological medication currently approved for SLE. Considering the merits of belimumab in the treatment of skin lesions in SLE, the patient was placed on intravenous belimumab and methylprednisolone (80 mg daily). After excluding any potential contraindications to biological therapy, such as acute infection or solid tumor(s), belimumab was administered intravenously at a dose of 10 mg/kg on days 0, 14, and 28, and every 4 weeks thereafter. Following 1 week of intravenous methylprednisolone therapy, cortisone was switched to oral prednisone (30 mg) for daily maintenance and was gradually reduced to 20 mg/day after two weeks. The bullous skin lesions steadily improved after three weeks (Figure 1B) and were completely cured at 9 months follow-up (Figure 1C, 1D). Subsequently, the patient was administered reduced oral steroids, and no relapse of her bullous skin lesions occurred after outpatient treatment. The patient tolerated belimumab well, and no side effects were observed during the entire 6-month follow-up period. In addition, laboratory investigations showed improvement (erythrocyte sedimentation rate, 15 mm/h; hemoglobin, 117 g/L; C3, 0.76 g/L; and C4, 0.106 g/L), while anti-dsDNA antibody, anti-nuclear antibodies, anti-nucleosome antibodies, and IgG turned negative 6 months later. The SLEDAI-2K was < 2. Details of treatment process and clinical indicators within four months can be seen in Figure 3.

Discussion

BSLE is a rare subtype of SLE, an autoimmune bullous skin disease (ABSD), that frequently...
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occurs in young women, with rare occurrence in childhood and adolescence\(^1\),\(^2\). The actual prevalence of childhood-onset BSLE has not been reported\(^6\),\(^13\), and no approved therapies for the treatment of BSLE are currently available.

Skin lesions develop in approximately 76% of patients with SLE, and less than 1% develop BSLE\(^{14}\). In a study\(^{15}\) involving 5,149 patients with cutaneous lupus, the incidence of BSLE was 0.19%. BSLE is defined as vesiculobullous skin eruptions in SLE that can occur before or following the diagnosis of SLE and must meet the American College of Rheumatology and/or Systemic Lupus International Collaborating Clinics diagnostic criteria for SLE\(^{16}\),\(^17\).

It is unknown whether BSLE flare-ups coincide with SLE activity. This condition is commonly linked with lupus nephritis and/or hematological abnormalities (anemia and/or leukopenia)\(^4\). Autoantibodies against type VII collagen are assumed to be responsible for the disease’s pathophysiology.

Furthermore, pathogenic autoantibodies may recognize epitopes in the amino-terminal non-collagenous region of collagen VII, causing blisters\(^{18}\). A study\(^{19}\) of BSLE patients identified critical autoantibodies at the basement membrane, including laminin-5, laminin-6, and bullous pemphigoid antigen I.

ABSDs are classified as intra-epidermal or sub-epidermal based on the target antigen and the location of bullae on the skin. BSLE is heterogeneous in nature and subcutaneous. According to the existing literature, linear IgA disease, toxic epidermal necrolysis, and herpes-like dermatitis are more prevalent in children. The differential diagnosis for these diseases can be clarified using histopathology and direct immunofluorescence\(^{20}\).

The primary treatment for BSLE is corticosteroid administration, both topical and systemic. In some cases, dapsone, MTX, HCQ, and biological agents have been shown to be effective in the treatment of BSLE\(^6\),\(^21\). Owing to persistent worsening of the patient’s skin lesions following the administration of traditional immunosuppressive medicines, it was difficult to wait for a thorough confirmation of the treatment response to these drugs. Additionally, refractory cases and intolerance to first-line systemic therapies present challenging situations\(^22\).

The deregulation of B-lymphocytes is a critical factor in the development of SLE\(^23\). Recently, biologics, such as rituximab, have been used to treat BSLE\(^{24}\), although with limited efficacy. Rituximab-induced persistent illness may be linked to increased levels of anti-dsDNA antibo-
dies, plasmocytes, and B-cell activation factors. However, rituximab is not an approved biological agent for SLE.

Belimumab is the only FDA-approved biological agent for the treatment of SLE. It is a monoclonal antibody against human IgG1 that blocks the binding of soluble BlyS to B cells, resulting in a reduction in the number of autoantibodies generated by B cells in the serum and achieving the goal of treating SLE.

Belimumab may be used for symptomatic treatment of patients with active SLE who exhibit acute mucocutaneous lesions, positive anti-dsDNA antibodies, and hypocomplementemia. Many management options are available for skin lesions in patients with SLE, including topical, systemic, and biological therapies. Among the biological therapies, there are moderate data supporting the use of belimumab.

Belimumab was added to the initial therapeutic regimen after obtaining informed consent from the patient and her parents, and the patient’s clinical improvement was strongly suspected to be attributed to the use of belimumab, since the patient completely recovered after belimumab treatment. To the best of our knowledge, this is the first report describing a case of refractory pediatric BSLE with SLE treated using a novel biological agent, without adverse effects.

Conclusions

In summary, addition of belimumab to the standard treatment in this case resulted in significant improvement in the signs and symptoms of refractory pediatric BSLE and SLE. Based on our results, belimumab may have potential value in the treatment of severe BSLE in cases confirmed to be resistant to traditional therapy. Nevertheless, it is necessary to further investigate the long-term effectiveness and safety of belimumab.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

This study was approved by Shenzhen Futian Hospital Ethics Committee of Shenzhen Futian Hospital for Rheumatic Diseases.

References

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