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CLINICAL CASE

# Bullous systemic lupus erythematosus: An uncommon manifestation in pediatric population

## Lupus eritematoso sistémico buloso: Una manifestación infrecuente en población pediátrica

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**What do we know about the subject matter of this study?**

Bullous Systemic Lupus Erythematosus (BSLE) is a rare variant of Systemic Lupus Erythematosus (SLE) and even more so in pediatrics. Although the prevalence of SLE is higher in the population of indigenous descent, it is not known whether this association occurs in BSLE.

**What does this study contribute to what is already known?**

To present a clinical case of a rare entity in pediatrics and report as a finding of interest the association between BSLE and Mapuche ethnicity, which could contribute to future studies evaluating its distribution in different ethnic groups.

## Abstract

Bullous systemic lupus erythematosus (BSLE) is an autoimmune subepidermal blistering disease secondary to the presence of autoantibodies against type VII collagen of the basement membrane zone. It is considered a variant of Systemic Lupus Erythematosus (SLE) and is uncommon in the pediatric population. **Objective:** To describe the case of a pediatric patient with a bullous eruption compatible with BSLE. **Clinical Case:** A 16-year-old female patient of Mapuche descent with history of SLE diagnosed at age 10, undergoing treatment. She consulted due to a six-week history of a generalized bullous eruption with no systemic symptoms. Biopsy for histology and direct immunofluorescence (DIF) confirmed the diagnosis of BSLE. The patient responded favorably to dapsone 100 mg/day (associated with her baseline treatment), without new reactivations after 8 years of follow-up. **Conclusion:** BSLE is an infrequent manifestation of SLE. The clinical presentation is similar to other bullous dermatoses, but the histopathology and DIF in correlation with the presence of SLE confirm the diagnosis. Although indigenous ancestry is associated with SLE high-risk alleles, studies regarding the association of BSLE in this ethnic group are still lacking.

**Keywords:**
Lupus Erythematosus Systemic;
Lupus Erythematosus Cutaneous;
Skin Diseases;
Vesiculobullous;
Dapsone

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## Introduction

BSLE is an autoimmune subepidermal blistering disease, considered a rare nonspecific cutaneous variant of SLE[1,2]. Although 59-85% of patients with SLE have cutaneous manifestations, less than 5% will present blistering lesions[3]. BSLE can occur throughout the disease and may be the first manifestation[4-6] and may or may not be associated with exacerbation of systemic involvement[7].

It is an uncommon pathology, with an annual incidence of 0.26 per million in adults[8], and it is even rarer in the pediatric population[1,4]. Like SLE, it mainly affects women of childbearing age[9].

Worldwide, the prevalence and incidence of SLE vary, with higher rates in some racial groups, including African Americans, Native Americans, and mixed races[10,11]. In fact, American Indian ancestry is associated with risk alleles for SLE[12], as well as early development of renal involvement[11]. Given the rarity of BSLE, there are no epidemiological studies in different racial groups to date.

In most cases, its pathogenesis is due to the presence of autoantibodies against type VII collagen, located at the dermal-epidermal junction (DEJ)[1,4]. The presence of these autoantibodies would activate the inflammatory cascade through the complement system, which would lead to neutrophil recruitment, resulting in proteolysis and the separation of the DEJ[13].

Clinically, it is characterized by an acute vesicular eruption or tense bullae on erythematous or healthy skin, predominantly on photo-exposed areas, and associated with mucosal involvement in 50% of the cases. The lesions evolve into crusted erosions that heal without scarring and may leave residual hypopigmented macules[1,4,6,7,14].

BSLE has distinctive histology, characterized by the presence of a subepidermal blister with abundant neutrophils. There is also an inflammatory cell infiltrate that may be accentuated in the dermal papillae or with a band-like distribution under the basement membrane[1,14]. Direct immunofluorescence (DIF) shows linear or granular deposition of all classes of immunoglobulins and the complement system in the DEJ[1].

The objective of this work is to describe the case of a pediatric patient with history of SLE and generalized blistering rash compatible with BSLE. This case is reported since it is an infrequent manifestation of SLE in the pediatric population and due to the interesting and illustrative clinical presentation.

## Clinical Case

16-year-old female patient of Mapuche descent, with history of SLE since the age of 10 years, without relevant family history. Initially, she was treated with prednisone and hydroxychloroquine (HCQ), with a good response and few reactivations during the first two years of therapy, when she required to start mycophenolate mofetil (MMF) due to joint activation.

While on treatment with MMF at 250 mg/day dose, HCQ 200 mg/day, and prednisone 2.5 mg/day, she attended the dermatology department with a 6-week history of generalized vesicular-bullous pruritic rash with oral and genital mucosal involvement. The patient had no fever nor associated systemic symptoms.

Physical examination showed multiple papulovesicular lesions on the neck, anterior trunk, arms, palms and dorsum of the hands, and soles; some were excoriated and eroded, associated with hypopigmented macules and tense bullae (figure 1). In the oral mucosa, there was a tense blister on the anterior edge of the tongue, and in the genital mucosa, there was a tense blister on the inner border of the left labium majus (figure 1).

Laboratory and imaging studies were performed to rule out systemic complications associated with SLE; blood count, erythrocyte sedimentation rate, C-reactive protein, complement system, renal function, urinalysis, and chest X-ray were normal. Given the history of SLE, we performed a biopsy of the lesions for histological study and DIF, with a presumptive diagnosis of BSLE.

Histologic study showed subepidermal vesicles with neutrophils, associated with accumulation of neutrophils in the papillary dermis, and superficial perivascular lymphocytic infiltrate compatible with subepidermal vesicular dermatitis with neutrophils (figure 2). DIF showed granular deposition of IgG, IgM, IgA, and C3 in the basement membrane (figure 2). Correlation of clinical, histopathologic, and DIF findings confirmed the diagnosis of BSLE.

Initial treatment consisted of increasing the doses of the baseline treatment to MMF 3 g/day, prednisone 25 mg/day, and HCQ 400 mg/day, achieving only partial control after 3 months. Due to a lack of response, dapsone was added at an initial dose of 50 mg/day for two months, presenting progressive improvement, however, new lesions kept occurring. After the increase to 100 mg/day, she presented total resolution of the lesions in 2 weeks. The patient completed 3 months of treatment, with no new reactivations after 8 years of follow-up.

## Discussion

BSLE is a nonspecific variant of SLE, considered a subepidermal autoimmune vesiculobullous disease.

The diagnosis of BSLE is based on the following criteria: (1) diagnosis of SLE according to the American

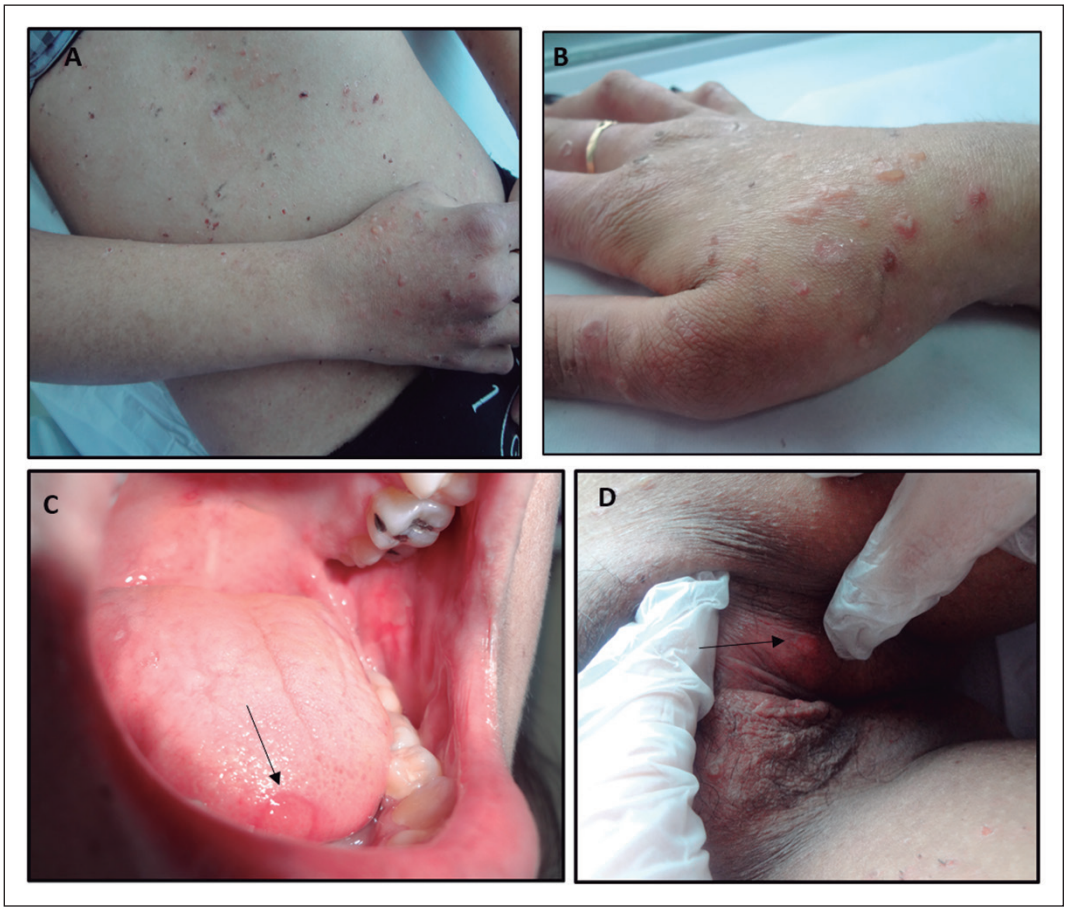


**Figure 1.** Mucocutaneous involvement. Multiple papulovesicular lesions on the abdomen and dorsum of hands, some excoriated and others eroded, associated with tense bullae (images A and B). In oral mucosa, there is a tense blister on the anterior edge of the tongue and erosion on the posterior palatal mucosa (image C). In the genital mucosa, there is a tense blister in the inner border of the left labium majus (image D).

College of Rheumatology criteria; (2) acquired vesiculobullous rash; (3) histologic confirmation of subepidermal blistering with a predominant presence of neutrophils in the dermis; (4) DIF with deposition of IgG and/or IgM and often IgA in the basement membrane; and (5) positive or negative DIF for circulating antibodies against type VII collagen[1].

Blistering diseases can occur isolated or associated with other systemic manifestations of SLE, particularly nephritis and serositis. Therefore, in the presence of BSLE, the presence of associated systemic involvement must be evaluated[15], which in our case did not exist.

In our patient, the history of SLE allowed us to easily make the diagnosis with the abovementioned criteria; however, there are cases in which the onset of the SLE occurs along with cutaneous manifestations. Therefore, when faced with an acquired bullous eruption of vesicles and/or tense bullae, other subepidermal bullous diseases such as linear IgA bullous dermatosis, dermatitis herpetiformis (DH), bullous pemphigoid (BP), and epidermolysis bullosa acquisita (EBA) should be considered within the differential diagnosis.

Linear IgA bullous dermatosis is the most common autoimmune blistering dermatosis of childhood. It is characterized by the presence of annular blisters in a "crown of jewels-like" pattern and the DIF showing linear IgA deposition in the DEJ[16]. DH presents with very pruritic papulovesicles, usually in extensor surfaces, with predominant IgA deposition in the DIF. BP is very rare in children, characterized by the presence of tense bullae (often associated with urticaria-like plaques) and histology with predominantly eosinophilic infiltrate. In EBA, in addition to tense bullae, there is usually skin fragility, atrophic scars, and milia, findings generally absent in BSLE[1,16,17].

Regarding the treatment, dapsone is considered the first-line therapy due to its effectiveness (demonstrated in 90% of cases)[17] and rapid onset of action, with cessation of new lesion formation in 24-48 hours and resolution of pre-existing lesions in 7-10 days[18]. However,

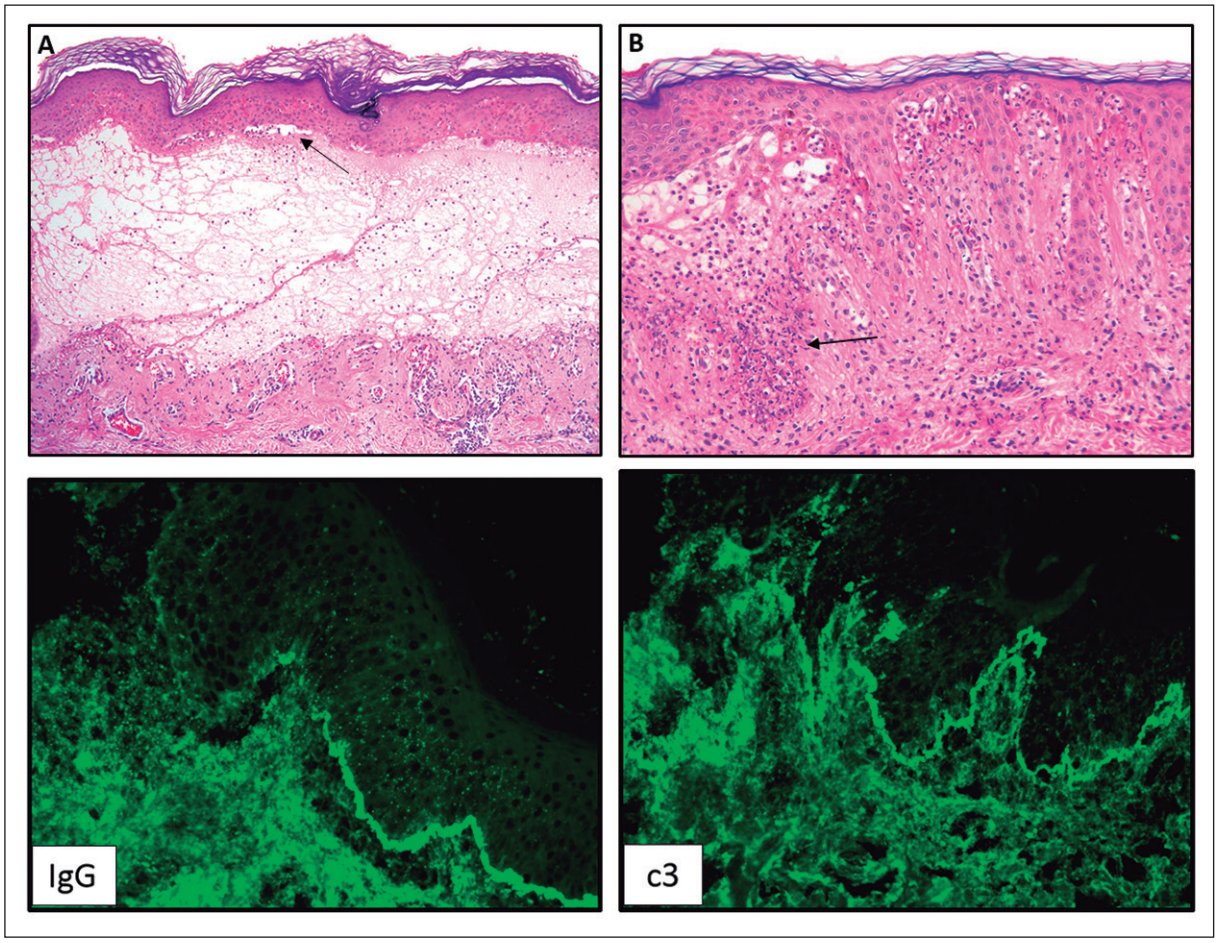


**Figure 2.** Standard histological examination and direct immunofluorescence. Subepidermal vesicles with neutrophils and cell debris (arrow image A), associated with neutrophils in the papillary dermis (arrow image B) and moderate superficial perivascular lymphocytic infiltrate. DIF shows granular deposition of IgG and C3 at the dermal-epidermal junction.

it should be noted that it presents a 23% of discontinuation rate due to adverse effects (mainly anemia, hepatitis, and hypersensitivity)[17]. Definitive discontinuation of treatment is usually possible after 12 months of disease evolution[1,18].

In patients already on SLE maintenance therapy with corticosteroids and/or immunosuppressants, increasing the dose of their baseline regimen has also been shown to be effective in controlling cutaneous blistering in some cases[1].

In patients with BSLE associated with systemic complications of SLE, treatment should include corticosteroids and/or immunosuppressants, and dapsone may be added for the management of skin lesions in refractory patients or those with very extensive involvement[1,3]. For those patients refractory to dapsone, prednisone, or immunosuppressants, the use of rituximab could be considered[3].

Since our patient was already under treatment for SLE, it was decided to increase the dose of her baseline regimen in order to avoid adding another drug. Due to the lack of response, it was decided to start dapsone at a dose of 50 mg/day, with partial improvement after 2 months. However, after increasing the dose to 100 mg/day, complete resolution of the lesions was observed after 2 weeks. The described dose of dapsone for the management of BSLE varies between 25 and 200 mg/day, with a recommended starting dose of 50 mg/day[1]. The dose in children is not established, but there are good results with doses of 1.5 mg/kg/day[15]. Therefore, after starting the administration of this drug, it is possible to increase the dose progressively until the expected response is achieved, as occurred in this case.

We report as a finding of interest the Mapuche ethnicity of our patient. Although it is known that SLE is more frequent in certain racial groups[12], the association between ethnicity and SLE has not been studied due to its low prevalence. This report could contribute to future studies that aim to evaluate ethnicity as a possible risk factor for this pathology.

## Conclusion

We present the case of a papulovesicular eruption in an adolescent girl of Mapuche descent with SLE, compatible with BSLE. The case is presented because it is an infrequent manifestation of SLE and should be considered among the differential diagnoses of bullous dermatoses. The differential diagnosis is broad and difficult to approach only from the clinical point of view, so histological and DIF studies are essential to reach the diagnosis and thus offer the best therapy. In addition, systemic involvement of associated SLE should be evaluated. Although a higher risk of SLE has been reported in a population of indigenous descent, there are no studies on the association of SLE in this ethnic group.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

## Financial Disclosure

Authors state that no economic support has been associated with the present study.

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