CASE REPORT

Bullous systemic lupus erythematosus - differential diagnosis with dermatitis herpetiformis *

Lúpus eritematoso sistêmico bolhoso - diagnóstico diferencial com dermatite herpetiforme

Wanessa Simão Barbosa[1]
Jackeline Gomes Guerra[2]
Luiz Fernando Fróes Fleury Júnior[4]
Camila Martins Rodarte[1]
Vanessa Gomes Maciel[3]
Maurício Barcelos Costa[5]

Abstract: Bullous systemic lupus erythematosus is a rare subset of systemic lupus erythematosus that is even rarer in pediatric patients. We report a case of a 12-year-old girl who presented with a vesiculobullous eruption on her face, neck, trunk and genital and oral mucosa, as well as anemia, sterile pyuria, ANA (1:1280, speckled pattern) and positive anti-Sm and anti-RNP. Pathological examination suggested dermatitis herpetiformis, and direct immunofluorescence revealed IgG, IgA and fibrin in the epithelial basement membrane zone. We present a typical case of bullous systemic lupus erythematosus and emphasize the importance of clinical and histopathological differential diagnosis with dermatitis herpetiformis.
Keywords: Autoimmunity; Dermatitis herpetiformis; Lupus erythematosus, Systemic; Skin Diseases; Type VII collagen; Vesiculobullous

Resumo: O lúpus eritematoso sistêmico bolhoso é um subtipo raro do lúpus eritematoso sistêmico, que ocorre ainda de forma mais incomum nos pacientes pediátricos. Relatamos o caso de uma adolescente de 12 anos, apresentando lesões vésico-bolhosas em face, pescoço, tronco, mucosas oral e genital, anemia, leucocitúria estéril, FAN: 1/1280 padrão nuclear pontilhado grosso, Anti-Sm e Anti-RNP positivos. O estudo anatomopatológico sugere dermatite herpetiforme e a imunofluorescência direta revela IgG, IgA e fibrina ao longo da zona de membrana basal. Apresentamos um caso típico de lúpus eritematoso sistêmico bolhoso e enfatizamos a importância do diagnóstico diferencial com a dermatite herpetiforme.
Palavras-chave: Auto-Imunidade; Colágeno tipo VII, Dermatite herpetiforme; Dermatopatias ; Vesiculobolhosas; Lúpus eritematoso sistêmico

Received on 25.10.2010.
Approved by the Advisory Board and accepted for publication on 04.12.2010.
* Study carried out at the Dermatology Service, Hospital das Clínicas, Federal University of Goiás (HC – UFG), Goiânia, GO, Brazil.
Conflict of interest: None / *Conflito de interesse: Nenhum*
Financial funding: None / *Suporte financeiro: Nenhum*

[1] Resident Dermatologist, Hospital das Clínicas, Federal University of Goiás (HC – UFG), Goiânia, GO, Brazil.
[2] Holder of a PhD in Dermatology from the Federal University of Rio de Janeiro (UFRJ) – Associate Professor, Department of Tropical Medicine and Dermatology, Institute of Tropical Pathology and Public Health, Federal University of Goiás (IPTSP - UFG) - Head of the Dermatology Service, Hospital das Clínicas, Federal University of Goiás (HC – UFG), Goiânia, GO, Brazil.
[3] Volunteer Lecturer, Department of Tropical Medicine and Dermatology, Institute of Tropical Pathology and Public Health, Federal University of Goiás (IPTSP - UFG)
[4] Holder of a master's degree in dermatology from the University of São Paulo School of Medicine (FMUSP) - Assistant Professor, Department of Tropical Medicine and Dermatology, Institute of Tropical Pathology and Public Health, Federal University of Goiás (IPTSP - UFG)
[5] PhD student and holder of a master's degree in pathology, Federal University of Goiás (UFG) - Head of the Pathology Department, Hospital das Clínicas, Federal University of Goiás (HC – UFG), Goiânia, GO, Brazil.

INTRODUCTION

Bullous systemic lupus erythematosus (BSLE) is a rare subtype of lupus erythematosus (SLE) that is quite uncommon during infancy, childhood and adolescence. [1, 2] Studies show that 76% of patients with SLE suffer from skin lesions during the course of the disease and that less than 5% of them present with bullous lesions. [3] In 23% of patients with SLE, skin lesions are the first manifestation[1].

Clinically, BSLE is characterized by a disseminated vesiculobullous skin rash that may or may not be limited to areas exposed to light. The blisters may be large and tense, as in bullous pemphigoid, or small and clustered together, as in dermatitis herpetiformis. They preferentially affect the torso and supraclavicular region but may also affect the mucosae, particularly in the mouth and pharynx. Small blisters on the vermilion border can be observed in 30% of cases. Patients may develop residual hyperpigmentation, and scars or milia may occasionally form. Pruritus may or may not be present. [4]

Histopathological examination reveals a subepidermal blister with neutrophilic microabscesses in the dermal papillae, perivascular inflammatory infiltrate composed of lymphomononuclear cells and, in some cases, leukocytoclastic vasculitis. The classic histological features of lupus erythematosus (LE), such as epidermal atrophy and hydropic degeneration of the basal cell layer, are absent in BSLE. Direct immunofluorescence reveals a linear or granular deposition of IgG, IgA and C3 in the basement membrane zone. [4]

CASE REPORT

A 12-year-old female patient was admitted with a complaint of tense vesiculobullous lesions, both isolated and in clusters, on her face, neck, torso and oral and genital mucosae on circinate and erythematous edematous plaques (Figures 1, 2, 3, 4). The patient also presented with asthenia, occasional fever and a general decline in her health, as well as very large axillary and cervical lymph nodes of 5 months duration. Laboratory tests revealed anemia (Hb - 8.7); sterile pyuria (66,000); ESR of 98mm; ANA (1/1280, coarse speckled nuclear pattern); positive anti-Sm and anti-RNP; and normal C3 and C4 levels. A biopsy of the skin lesion was carried out, and the pathological findings included a subepidermal blister with neutrophilic microabscesses in the dermal papillae suggestive of dermatitis herpetiformis (Figure 4). Direct immunofluorescence revealed IgG, IgA and fibrin deposits along the basement membrane zone. Histopathological examination of the sample from the cervical lymph node biopsy revealed reactive lymphoid hyperplasia. Gluten intolerance was also investigated, and the results were negative for IgA anti-

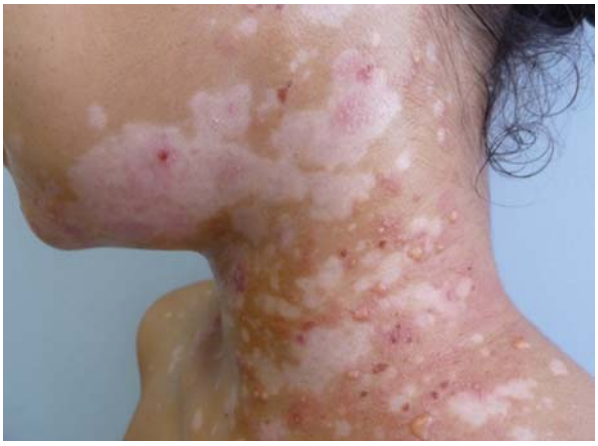

Figure 1: Tense vesicubullous lesions on an erythematous, edematous base

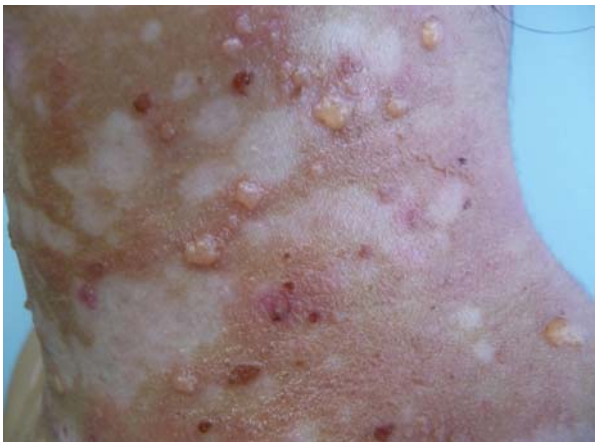

Figure 2: Vesicles and blisters, both isolated and in clusters

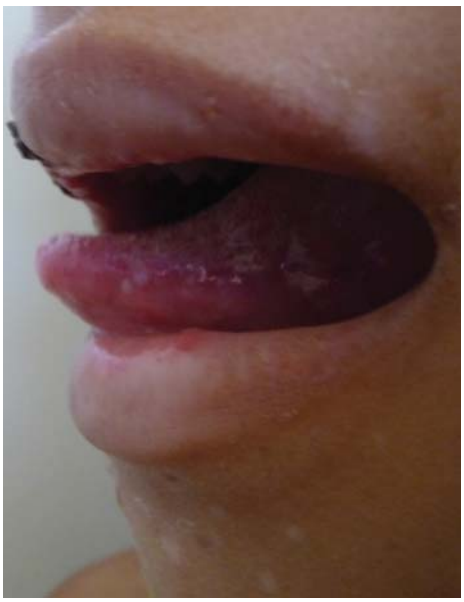

Figure 3: Ulceration on the vermilion border and side of the tongue

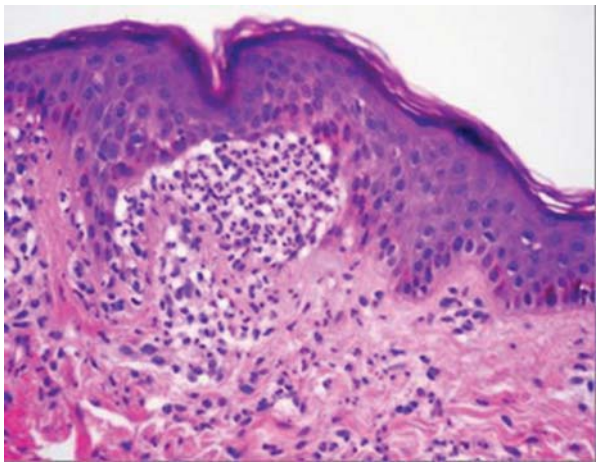

FIGURE 4: HE. Neutrophilic microabscess in a dermal papilla

gliadin, IgG anti-gliadin, anti-endomysium and anti-tissue transglutaminase antibodies.

After diagnosis, treatment for BSLE was started with dapsone 50 mg/day together with prednisone 20 mg/day (body weight – 32.5 kg) and the patient's lesions healed completely after 1 month. Prednisone was then reduced gradually, and dapsone was continued in the 50 mg/day dose.

DISCUSSION

BSLE is a rare disease that has an incidence of less than 0.2 cases per million per year and represents only 2 to 3% of autoimmune subepidermal bullous dermatoses. It is an acquired bullous disease caused by anti-type VII collagen antibodies. [5]

Bullous eruptions are rare skin manifestations in SLE. [6,7]Although bullous lesions are known to be very closely related to SLE, the activity of the bullous disease may or may not coincide with that of the systemic disease. [5,8] In most cases there is remission without any complication in less than a year. [9,10]

BSLE is a bullous form of SLE with a distinct set of clinical and immunopathological characteristics. [6]

Camisa and Sharma[11] proposed the following criteria for diagnosing BSLE:

(1) a diagnosis of SLE based on the American Rheumatism Association criteria;
(2) the presence of vesicles or blisters in areas exposed to the sun, but not limited to these areas;
(3) histology compatible with a diagnosis of dermatitis herpetiformis;
(4) negative indirect immunofluorescence for circulating anti-basement membrane antibodies;
(5) positive direct immunofluorescence for IgG or IgM or both as well as for IgA in the basement membrane zone.

Bullous lesions in a patient with SLE leads to two important diagnoses: BSLE and SLE with blisters. [10]

SLE with blisters is characterized by polycyclic lesions with blisters on the edges. The blisters are confined to areas exposed to the sun and may form scars. [10] In the histopathological examination, intense hydropic degeneration of the basal cell layer, edema of the upper dermis and occasional epidermal necrosis can be observed. Blisters are formed as a result of severe damage to the basal layer and consequent separation of the basement membrane from keratinocytes. Anti-type VII collagen antibodies are not formed. [10] IgG and IgM deposits in the basal membrane zone may be formed. Ultraviolet radiation, high anti-Ro antibody titers, deposition of immune complexes and abnormal cellular immunity are considered to be responsible for damage to the basal layer. [10]

The main differential diagnoses for BSLE are epidermolysis bullosa acquisita (EBA), dermatitis herpetiformis (DH), bullous pemphigoid (BP) and linear IgA bullous dermatosis.

It is important to remember that in both EBA and BSLE, anti-type VII collagen antibodies are present in the sublamina densa of the basement membrane zone and that both conditions have similar genetic characteristics as they are both associated with the HLA-DR2 antigen. [9] However, the diseases progress differently, as BSLE can very often be cured within a year whereas EBA has a longer course and does not meet the criteria for SLE. [10]

Although the clinical and histopathological features of DH can be the same as those of BSLE, DH can be differentiated from BSLE by the presence of markers of gluten sensitivity: anti-gliadin, anti-endomysium and anti-tissue transglutaminase antibodies. [7] In addition, direct immunofluorescence shows granular, fibrillar or punctate IgA deposits concentrated in the dermal papillae and along the basement membrane zone.

In BSLE, IgA deposits can occur in 65% of cases, in contrast with 13% of cases in SLE without bullous lesions. [7] Camisa[11] established a relationship between IgA deposits and disease activity, while Miller et al. established a relationship with an increased incidence of kidney damage. [7] In BSLE, IgG and IgM can be found in addition to IgA in the basement membrane zone, allowing this condition to be easily differentiated from DH, in which only IgA deposits are observed.

The most effective treatment for BSLE is with dapsone, which generally produces a fast response, even in small doses (25 to 50 mg/day). [5,10] Dapsone has an inhibitory effect on the myeloperoxidase-hydrogen peroxidase-halide system of neutrophils, leading to a

decrease in production of proinflammatory oxygen intermediates by neutrophil activation. [12] In addition, dapsone prevents cyclooxygenase-mediated production of prostaglandin E2[1].

Patients with glucose-6-phosphate dehydrogenase deficiency may present with severe hemolysis when taking dapsone. Patients should therefore be tested for this deficiency before being treated with this drug. Hemoglobin levels in many patients can drop by 1 to 2 g/dL after treatment has started. They can be partially restored with concomitant use of 4000 IU of vitamin E once a day. [13] Other collateral effects include methemoglobinemia, motor neuropathy, exfoliative dermatitis, hepatitis, headache, gastrointestinal disorders and, rarely, agranulocytosis. Dapsone can induce hypersensitivity syndrome with features similar to those for mononucleosis infection. The syndrome generally starts 4 to 6 weeks after first treated. The symptoms associated with the syndrome are pruritus, fever, general indisposition, raised ESR, enlarged lymph nodes and lymphocytosis. [12]

Colchicine is a therapeutic option for neutrophil-mediated bullous diseases. It interferes with the chemotaxis of neutrophils and the release of lysosomal enzyme by polymorphonuclear cells. The commonest side effects are temporary diarrhea and abdominal discomfort. Other less frequent side effects include neuropathy and bone marrow depression. [14]

The bullous lesions in LE do not respond to treatment with only systemic corticosteroids. Adjuvant therapies must also be used in cases that do not respond to or are intolerant of dapsone; the use of azathioprine, antimalarial agents, mycophenolate mofetil and cyclophosphamide has been reported in the literature. [5,10] In one case report, Malcangi et al.[15] found that methotrexate in a small dose (10 mg/week) was effective in controlling BSLE.

The case described here illustrates the typical signs and symptoms of bullous systemic lupus erythematosus and draws attention to the need for clinical and histopathological differential diagnosis with dermatitis herpetiformis. ❑

REFERENCES

1. Harris-Stith R, Erickson QL, Elston DM, David-Bajar K. Bullous eruption: a manifestation of lupus erythematosus. Cutis. 2003;72:31-7.
2. Fujimoto W, Hamada T, Yamada J, Matsuura H, Iwatsuki K. Bullous Systemic Lupus Erythematosus as an Initial Manifestation of SLE. J Dermatol. 2005;32:1021-7.
3. Yell JA, Allen J, Wojnarowska F, Kirtschig G, Burge SM. Bullous systemic lupus erythematosus: revised criteria for diagnosis. Br J Dermatol. 1995;132:921-8.
4. Obermoser G, Sontheimer RD, Zelge B. Overview of common, rare and atypica manifestations of cutaneous lupus erythematosus and histopathological correlates. Lupus. 2010;19:1050-70.
5. Tincopa M, Puttgen KB, Sule S, Cohen BA, Gerstenblith MR. Bullous lupus: an unusual initial presentation of systemic lupus erythematosus in an adolescent girl. Pediatr Dermatol. 2010;27:373-6.
6. Bittencourt AL, Dias NFC, Sadigursky M. Lupus Eritematoso Sistêmico Bolhoso: apresentação de um caso infantil. An Bras Dermatol. 1988;63:85-8.
7. Oliveira VM, Cernea SS, Sotto MN, Vilela MAC. Lúpus eritematoso sistêmico bolhoso: estudo de dois casos e revisão da literatura. An Bras Dermatol. 1990; 65:23S-28S.
8. Cotell S, Robinson ND, Lawrence C. Autoimmune blistering skin diseases. Am J Emerg Med. 2000;18:288-99.
9. Vieira FMJ, Oliveira ZNP. Lúpus eritematoso sistêmico bolhoso. An Bras Dermatol. 1998;73:143-7.
10. Yung A, Oakley A. Bullous systemic lupus erythematosus. Australas J Dermatol. 2000;41:234-7.
11. Camisa C, Sharma HM. Vesiculobullous systemic lupus erythematosus. Report of two cases and a review of the literature. J Am Acad Dermatol. 1983;9:924-33.
12. Paniker U, Levine N. Dapsone and sulfapyridine. Dermatol Clin. 2001;19:79-86.
13. Glied M, Rico MJ. Treatment of autoimmune blistering diseases. Dermatol Clin. 1999;17:431-40.
14. Cunningham B, Kirchmann T, Woodley D. Colchicine for epidermolysis bullosa acquisita. J Am Acad Dermatol. 1996;34:781-4.
15. Malcangi G, Brandozzi G, Giangiacomi M, Zampetti M , Danieli MG. Bullous SLE: response to methotrexate and relationship with disease activity. Lupus. 2003;12:63-6.

Mailing Address / Endereço para correspondência:
Wanessa Simão Barbosa
Primeira Avenida, s/n - Setor Leste Universitário
74605 020 Goiânia GO) Brazil
E-mail: wanessasimao@yahoo.com.br

How to cite this article/*Como citar este artigo*: Barbosa WS, Rodarte CM, Guerra JG, Maciel VG, Fleury Jr LFF, Costa MB. Bullous systemic lupus erythematosus - differential diagnosis with dermatitis herpetiformis. An Bras Dermatol. 2011;86(4 Supl 1):S92-5.