

Widespread vesiculobullous eruption in a 16-year-old male

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SUMMARY

Bullous systemic lupus erythematosus (BSLE) is a rare but distinct disease, characterized by vesiculobullous skin eruptions in systemic lupus erythematosus (SLE). It can arise either before or after a diagnosis of SLE has been established. BSLE is characterized by a dermatitis herpetiformis-like histology and an autoimmunity to type VII collagen. It must be differentiated from other autoimmune vesiculobullous diseases such as epidermolysis bullosa acquisita, dermatitis herpetiformis, linear IgA disease, and bullous pemphigoid. A combination of clinical, histological, and immunofluorescence findings are necessary to establish a diagnosis of BSLE. We present a case of BSLE to illustrate and emphasize the need for an integrative diagnostic approach.

Introduction

Bullous systemic lupus erythematosus (BSLE) is a rare dermatosis that is regarded as a distinct variant of systemic lupus erythematosus (SLE) (1–4). It is characterized by widespread vesiculobullous eruptions, a dermatitis herpetiformis-like histology, immunologic features resembling epidermolysis bullosa acquisita (EBA), and striking response of cutaneous lesions to dapsone treatment. We present a case of BSLE to illustrate and emphasize the need for an integrative diagnostic approach, to include clinical, histological, and immunofluorescence findings.

Case report

A 16-year-old boy presented in June 2007 with “butterfly” facial erythema, accompanied by vesicles

and bullae. Similar lesions subsequently developed on the trunk and proximal parts of the upper extremities. The vesicles and bullae quickly ruptured and crusted (Fig. 1). Oral ulcers developed in July 2007. The patient had an elevated body temperature up to 39 °C for three weeks before being admitted to the rheumatology department at the end of July 2007. Apart from the changes to his skin described above, physical examination showed no abnormalities. The results of laboratory tests revealed a mildly elevated sedimentation rate (32 mm/h; normal <15 mm/h), normal C-reactive protein levels (< 5mg/l), leucopenia ($1.3 \times 10^9/l$; normal $4.0\text{--}10.0 \times 10^9/l$), mild thrombocytopenia ($105 \times 10^9/l$; normal $140\text{--}340 \times 10^9/l$), mild Coombs positive anemia (106 g/l; normal 140–180 g/l), and proteinuria (0.77 g / 24 hours). Immunological blood testing showed positive antinuclear antibodies (titer > 1:640), whereas the patient was shown

KEY WORDS

bullous systemic lupus erythematosus, bullous skin disease, dermatitis herpetiformis, epidermolysis bullosa acquisita



Figure 1. Vesiculobullous lesions with crusting arising from an area affected by erythema on the face (a), trunk, and proximal parts of the upper extremities (b). Note the “butterfly” facial erythema.

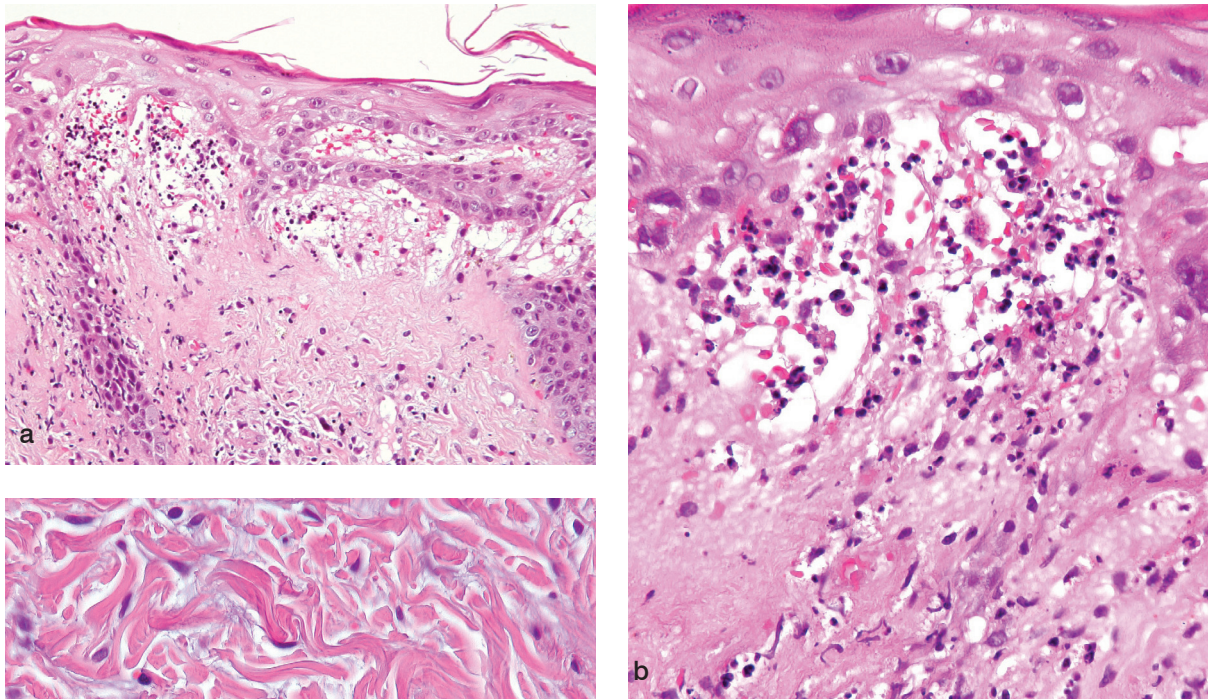


Figure 2. Subepidermal vesicle containing neutrophils, fibrin, and nuclear dust with mild inflammatory infiltrate in the dermis (a, b), and deposition of mucin in the reticular dermis (c).

to be negative for antibodies against soluble nuclear antigens, dsDNA, cardiolipin, and beta2-glycoprotein I. Lupus anticoagulant was negative. Two episodes of convulsions developed on the third day of admission, which were successfully treated with sedation.

A skin biopsy from a lesion on the shoulder was performed in July 2007. The histology revealed subepidermal clefting with the formation of subepider-

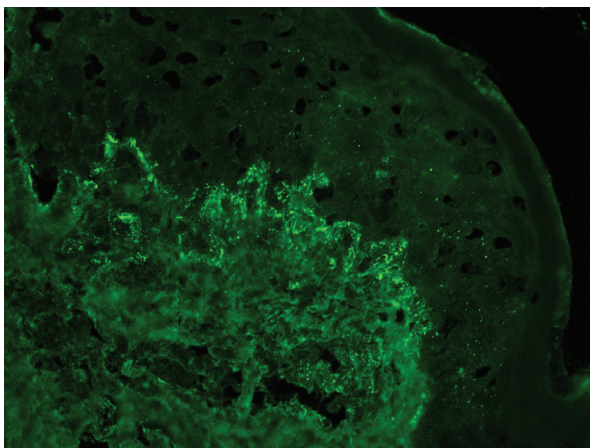


Figure 3. Granular deposition of IgG along the epidermal basement membrane.

mal vesicles containing fibrin, neutrophils, and nuclear dust (Figs. 2a and 2b). In addition, neutrophilic microabscesses were present in the papillary dermis. The epidermis showed focal interface changes with vacuolar degeneration and apoptosis of basal keratinocytes. In the dermis, there was a mild perivascular and perifollicular infiltrate composed of lymphocytes, macrophages, and neutrophils. A deposition of mucin was demonstrated in the dermis by alcian blue histochemical staining (Fig. 2c). Direct immunofluorescence revealed a granular deposition of IgG, IgA, IgM, and complement components C1q and C3 along the epidermal basement membrane and within the vessel walls of the superficial dermis (Fig. 3).

Based on clinical, histopathological, and immunofluorescence findings, the diagnosis of BSLE was established. Therapy was commenced using 6-methylprednisolone and pulse cyclophosphamide (1 g monthly for six months), followed by mycophenolate mofetil 1 g bid, which was administered for one year and then discontinued. The skin and oral lesions regressed, the proteinuria disappeared, and there were no further convulsions. Two years after the onset of the disease he remains in full remission on low-dose corticosteroids and hydroxychloroquine.

Discussion

Patients with SLE rarely (in less than 1%) develop widespread vesiculobullous eruptions that cannot be classified as either of the primary bullous dermatoses and are not merely a manifestation of extreme basal cell hydropic degeneration and the resulting epidermal-dermal separation. In such cases, it is referred to as BSLE, a unique dermatosis that is regarded as a distinct variant of SLE (1–4). It is characterized by dermatitis herpetiformis-like histology, immunologic

features resembling EBA, and a striking response of cutaneous lesions to dapsone treatment.

Similarly to SLE, BSLE most often affects young patients, predominantly female, in the second to fourth decades of life. Although any sun-exposed or non-sun-exposed areas can be affected, the upper trunk, neck, supraclavicular areas, and proximal extremities are predilection sites (1, 2). The skin eruption comprises bullae arising either from areas affected by diffuse erythema or on an urticarial base resembling bullous pemphigoid, or as grouped vesicular lesions mimicking dermatitis herpetiformis (1, 2, 4). The onset of vesiculobullous cutaneous lesions can precede, coincide with, or follow the diagnosis of SLE, as defined by the revised American Rheumatism Association criteria for classification of SLE (3, 5). Our patient met several diagnostic criteria: skin lesions including malar rash, oral ulcers, renal, hematological, and neurological disorders, and a positive result for antinuclear antibodies. The patient was treated with systemic corticosteroids and pulse cyclophosphamide, followed by mycophenolate mofetil due to the severe systemic involvement, and did not receive dapsone treatment.

Bullous changes in lupus erythematosus have two basic histological patterns: neutrophilic and mononuclear (6). The neutrophilic pattern typical of BSLE is characterized by subepidermal vesicles or bullae containing fibrin, mixed inflammatory cell infiltrate with a predominance of neutrophils, and nuclear debris. These histological features simulate dermatitis herpetiformis or linear IgA disease (1). In contrast to dermatitis herpetiformis and linear IgA disease, BSLE frequently includes the deposition of mucin in the dermis. On the other hand, bullous changes with a mononuclear inflammatory pattern can develop in the cutaneous lesions of lupus erythematosus as a result of extensive damage to the epidermal basal layer. This is due to intense interface dermatitis, which can result in epidermal-dermal separation and vesicle formation. Such bullous changes, which can clinically resemble erythema multiforme or toxic epidermal necrolysis, represent a spectrum of changes resulting from cutaneous lupus erythematosus and are not referred to as BSLE (1, 6).

Patients with SLE can produce a myriad of autoantibodies, resulting in diverse clinical manifestations. Similarly to EBA, the pathogenesis of BSLE is associated with autoantibodies reacting with collagen type VII (2, 4). Multiple classes of immunoglobulins are often detected along the basement membrane by direct immunofluorescence: IgG has been found in nearly 100% of patients with BSLE, IgA in about 70%, and IgM in 50%. Deposition of immunoreactants along the basement membrane has been reported to be

granular in 40% of cases, similar to the lupus band in non-bullous cutaneous lupus, or linear in 60%, similar to the deposits in bullous pemphigoid or EBA (1, 3). In addition to deposits along the basement membrane, deposition of immunoreactants within vessel walls can be identified in BSLE (1).

The differential diagnosis of BSLE includes other autoimmune vesiculobullous diseases such as EBA, dermatitis herpetiformis, linear IgA disease, and bullous pemphigoid (1, 3–6). EBA generally occurs in

older patients than does BSLE, and it is associated with the formation of bullae at the sites of previous trauma or mechanical rubbing. These bullae heal with scarring and do not respond to dapsone treatment. Despite similar histological features, dermatitis herpetiformis can be distinguished from BSLE by observing granular deposits of IgA in dermal papillae (3). Linear IgA dermatosis is characterized by the linear deposition of IgA along the basement membrane in perilesional skin (5).

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