Bullous Systemic Lupus Erythematosus With Milia and Calcinosis

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Bullous systemic lupus erythematosus (SLE) is a rare skin manifestation of SLE. It shares many features with epidermolysis bullosa acquisita (EBA). We report on a patient with SLE who developed a vesiculobullous eruption followed by findings not typical in bullous SLE, namely milia, mild scarring, and calcinosis. We discuss the relationship between bullous SLE and EBA.

Bullous systemic lupus erythematosus (SLE) is characterized by a chronic, widespread, blistering eruption that is nonscarring. It also features a subepidermal blister with neutrophil-predominant infiltrate in the upper dermis without vacuolar interface dermatitis. Direct immunofluorescence (DIF) shows evidence of the specific changes of SLE, ie, immunoglobulin and complement deposition at the basement membrane zone (BMZ) that are ultrastructurally localized on or beneath the lamina densa.[1] Some patients have circulating antibodies that are similar to epidermolysis bullosa acquisita (EBA) antibodies, ie, they recognize collagen VII molecules of the anchoring fibrils and bind the dermal side of salt-split skin by indirect immunofluorescence (IIF).

EBA, classically described as a mechanobullous disorder,[2] has a heterogeneous clinical presentation including an inflammatory type[3-10] that is clinically, histologically, and immunologically similar to bullous SLE. Because of the similarities, some authors have suggested that bullous SLE represents EBA in a patient with SLE.[11] Subtle differences between the two conditions exist. These include the association of milia and scarring with EBA but not with bullous SLE. In addition, the pattern of fluorescence in EBA is homogeneous, while in bullous SLE it may be either homogeneous or granular.

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We report a patient with SLE who developed a vesiculobullous eruption that was subsequently associated with milia, mild scarring, and calcinosis.

Case Report

A 26-year-old black woman with a 6-year history of SLE was referred for evaluation of a vesiculobullous eruption. The eruption began 8 months previously as pruritic vesicles over the elbows and knees that spread to involve the hands, trunk, and later the lips. She was receiving prednisone (20 mg twice a day), hydroxychloroquine (200 mg/d), and a superpotent topical steroid. Results of a skin examination revealed a generalized eruption consisting of vesicles, bullae, edematous plaques, and erosions over the lips, buccal mucosa, hands and feet (including palms and soles), elbows, knees, and trunk (Figure 1). Results of a histopathologic evaluation showed a subepidermal blister with a dense diffuse neutrophilic infiltrate at the dermal-epidermal junction, focal neutrophilic abscesses in the papillary dermis, and single neutrophils along the dermal-epidermal junction (Figure 2). DIF of healthy skin showed intense homogeneous and clumped deposition of IgG and moderate deposition of IgA, IgM, and C3 along the epidermal BMZ. IIF using salt-split skin as substrate showed no antibodies against the BMZ.

Results of a complete blood count showed a hemoglobin level of 11.0 g/dL and a hematocrit level of 33.5%. Reticulocyte count was high (5.0%, reference range 0.5%–2.0%). Total leukocyte count was 9800 cells/mm^3 with 89% neutrophils, 9% lymphocytes, and 2% monocytes. Results of a urinalysis were normal, and levels of serum creatinine, blood urea nitrogen, aspartate aminotransferase, alanine aminotransferase, phosphorus, and calcium levels were all within reference ranges. Antinuclear antibody results were positive (1:1280, homogeneous), as were antibodies to nuclear DNA (by IIF using crithidia) and Ro/SSA (by double immunodiffusion). Serum studies for antibodies to La/SSB, nuclear RNP, and Sm were negative.

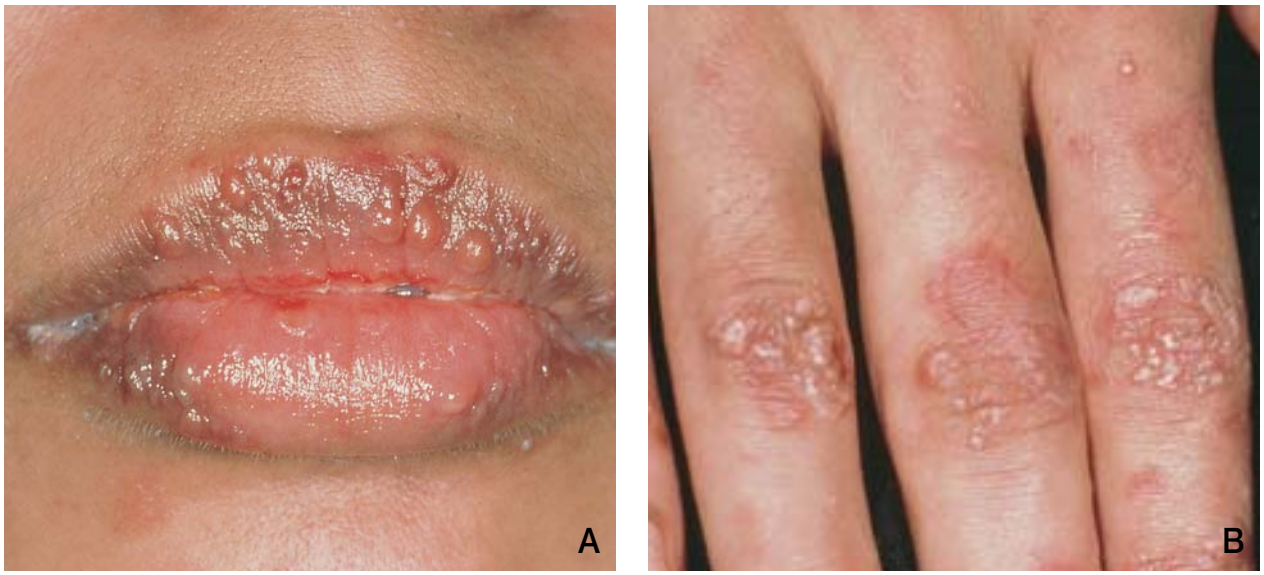

Figure 1. Bullous systemic lupus erythematosus with (A) intact vesicles on the lips and (B) several milia and few vesicles.

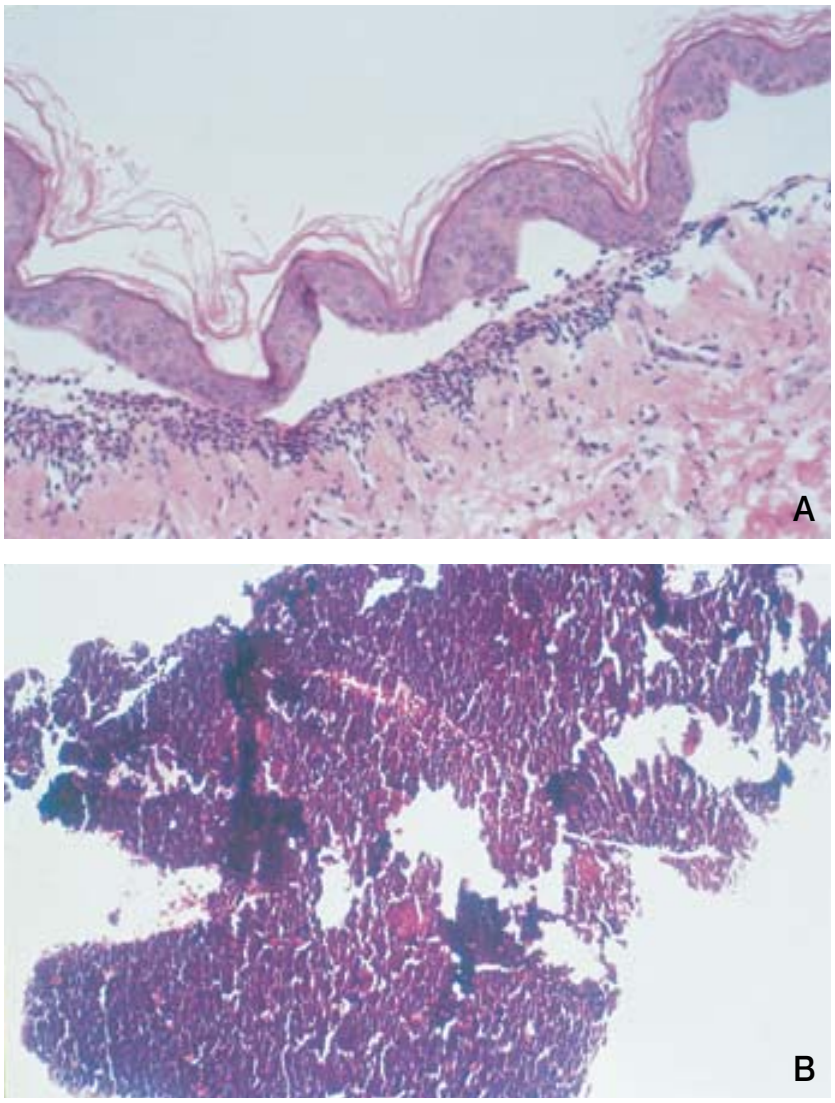

Figure 2. Light microscopy: (A) a subepidermal vesicle with a dense diffuse infiltrate of neutrophils at the base (H&E, original magnification ×200), and (B) a papule over the palmar side of a finger reveals calcified tissue (H&E, original magnification ×100).

Comparison of Inflammatory Epidermolysis Bullosa Acquisita and Bullous Systemic Lupus Erythematosus*

	Inflammatory EBA	Bullous SLE
Histology	Moderate to intense mixed cellular infiltrate composed of neutrophils, monocytes, and eosinophils; neutrophils predominate	Same; dermal papillary micro-abscesses also may be present
Electron microscopy	Immune deposits located beneath the lamina densa	Same
Direct immunofluorescence	Linear IgG, C3 at BMZ; IgA and IgM also may be seen	60% linear pattern similar to EBA; 40% granular pattern
Indirect immunofluorescence on salt-split skin	IgG anti-BMZ binds dermal side of salt-split skin in 50% of patients	Same
Western blot analysis	Antibodies to type VII collagen	Same
Response to dapsone	Variable[9,10,12]	Good
Scarring and milia	May or may not be present[4,5,9,10]	Not previously described
HLA	DR2	DR2

*EBA indicates epidermolysis bullosa acquisita; SLE, systemic lupus erythematosus; BMZ, basement membrane zone; HLA, histocompatibility locus A.

Because of the extensive nature of the lesions, treatment was initiated with intravenous pulse steroid followed by progressively increasing doses of dapsone, starting with 75 mg/d and increasing to 225 mg/d. The patient had complete resolution of the lesions within a few weeks. Hydroxychloroquine and topical steroid were discontinued. Prednisone was tapered off over 6 months as the dapsone dosage was increased. After one year of treatment, dapsone was tapered over 5 months without recurrence of lesions. During the course of treatment, multiple milia and mild scarring on the hands were noted. Multiple, discrete, white chalky papules were noted on the tips of some fingers one month after discontinuation of dapsone. Histologic evaluation of one of the lesions revealed focal calcinosis (Figure 2).

Comment

Our patient had SLE with neutrophil-mediated subepidermal blisters that responded to dapsone and resolved with milia, mild scarring, and calcinosis. This patient represents atypical bullous SLE with scarring manifested by milia and calcinosis. Some authors have proposed that bullous SLE represents inflammatory EBA in a patient with SLE. Bullous SLE and inflammatory EBA are closely related (Table). Patients with EBA frequently develop manifestations of scarring such as milia formation. To our knowledge, there are no previous reports of milia or scarring in bullous SLE. It is not surprising that lesions of bullous SLE that have a pathomechanism similar to inflammatory EBA may develop scarring, as seen in our patient. It is interesting that the literature describes 4 patients who had EBA preceding SLE. Two of the 4 patients had generalized inflammatory lesions that responded to dapsone.[3,13] In retrospect, these patients had bullous SLE.

To our knowledge, this case represents the first report of calcinosis cutis occurring in bullous SLE. Calcinosis cutis is a common feature of dermatomyositis and scleroderma but is rarely seen in SLE[14-27] and has not been reported in EBA. The

pathophysiology of calcinosis cutis in our patient is not clear; however, it most likely represents postinflammatory dystrophic calcification. Phosphate bound to the denatured proteins of necrotic cells at sites of trauma or inflammation may serve as a nidus for calcification.[28] Our case of a patient with bullous SLE associated with milia and calcinosis supports the hypothesis that bullous SLE and EBA are closely related.

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