Bullous lupus erythematosus (BSLE) is a rare subset of systemic lupus erythematosus (SLE), often associated with autoimmunity to type VII collagen. Generally, patients with BSLE meet the criteria for SLE as defined by the American College of Rheumatology. We present a case of a 17-year-old adolescent girl who presented with a vesiculobullous eruption without detectable type VII collagen antibodies and without full criteria for SLE. Differential staining was characteristic for lupus erythematosus (LE), suggesting her eruption is related to LE. We review the spectrum of bullous disease in patients with LE and discuss the pathogenesis and histology of these eruptions, as well as current therapeutic options.


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CONTINUING MEDICAL EDUCATION

GOAL
To gain a thorough understanding of bullous lupus erythematosus (BSLE)

OBJECTIVES
Upon completion of this activity, dermatologists and general practitioners should be able to:
1. Discuss the clinical and histologic presentations of BSLE.
2. Examine the differential diagnosis for BSLE.
3. Outline treatment options for BSLE.

CME Test on page 38.

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This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom, Inc. Albert Einstein College of Medicine is accredited by the ACCME to provide continuing medical education for physicians. Albert Einstein College of Medicine designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician’s Recognition Award. Each physician should claim only that hour of credit that he/she actually spent in the activity. This activity has been planned and produced in accordance with ACCME Essentials.

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Bullous Eruption

Bullous systemic lupus erythematosus (BSLE) is a rare subset of systemic lupus erythematosus (SLE) associated with autoimmunity to type VII collagen. BSLE is an autoimmune-mediated, chronic, widespread, non-scarring, subepidermal blistering skin disease occurring in patients with SLE. In 23% of patients with SLE, cutaneous involvement is the initial manifestation. Approximately 76% of patients with SLE will have skin changes at some stage during the course of their disease. Among these patients, fewer than 5% will have chronic vesicobullous lesions. Generally, patients with BSLE meet the criteria for SLE as defined by the American College of Rheumatology (ACR) and have a widespread vesicobullous eruption that is generally unrelated to the severity of the SLE. Some patients have bullous eruptions related to lupus erythematosus (LE) but do not meet ACR criteria for SLE. We present such a patient and discuss the spectrum of bullous disease in patients with LE.

Case Report

A 17-year-old African American adolescent girl presented with a 2-day history of a blistering eruption with an abrupt onset. Physical examination revealed photodistributed tense bullae. Innumerable beadlike vesicles coalescing into larger bullae were noted on her face, with dramatic involvement of her lips and ears (Figures 1 and 2). Larger bullae on urticarial bases were found on her upper torso. Initially, no mucosal involvement was noted; however, within days, the patient developed oral and vaginal erosions. In the preceding 5 months, she had occasionally experienced a few blisters on her face but had otherwise been healthy. The patient was feeling well at the time of presentation and was not taking any medication except for a methylprednisolone dose pack prescribed during her visit to the emergency department the previous evening.

Results of a shave biopsy of an intact bulla revealed a neutrophil-rich subepidermal bulla with neutrophils stuffing the dermal papillae and lined up along the dermal-epidermal junction (DEJ) (Figure 3). There was no leukocytoclastic vasculitis and no eosinophils were noted. Results of direct immunofluorescence (DIF) revealed IgG 4+ granular/continuous granular staining at the DEJ, trace IgM with 1+ staining of colloid bodies at the DEJ, 2+ granular/continuous granular C3 staining at the DEJ, and 3+ granular/continuous granular C1q staining at the DEJ (Figure 4). The specimen was negative for IgA. Laboratory investigation revealed an antinuclear antibody of 1:160; anti-DNA of 1:265 (negative is <200); and negative ribonuclear protein antigen, Smith antigen, Sjögren syndrome A and B antigens, and lupus anticoagulant and anticoagulant antibodies. Results of complete blood cell count (CBC), blood chemistry, and urinalysis were within reference range. No type VII collagen antibodies were found.

Treatment with oral steroids had begun prior to the patient presenting to dermatology, and no improvement was noted during a 1-week period. In anticipation of starting dapsone, a glucose-6-phosphate dehydrogenase level was ordered, and colchicine was begun at a dose of 0.6 mg 2 times a day. The bullous lesions showed some response within 2 days. The patient was subsequently switched to dapsone; however, colchicine was reinstituted after she developed symptoms consistent with dapsone hypersensitivity, including a diffuse pruritic morbilliform eruption, nausea, and abdominal pain, with elevated liver enzyme levels—ascparate aminotransferase was 304 U/L (reference range, 0–37 U/L) and alanine aminotransferase was 360 U/L (reference range, 0–40 U/L). The eruption was eventually controlled with 0.6 mg of colchicine 3 times a day and prednisone. After multiple failed attempts to taper prednisone, 400 mg of hydroxychloroquine once a day was added. After 2 months, the patient was able to tolerate the steroid taper without a rebound flare of bullous lesions.

Comment

BSLE typically presents in the second or third decade of life. Patients with BSLE seldom have discoid lesions or annular erythema. Lesions may form large blisters on the trunk that resemble the lesions of bullous pemphigoid. Bullous skin lesions also may appear on flexural and extensor surfaces with a preference for sun-exposed areas. Bullae may form on an erythematous base or on normal skin. Some skin lesions present as herpetiform vesicles with clusters of ulcers. Because of the herpetiform grouping and dermatitis herpetiformlike histology, dermatitis herpetiformis should be included in the differential diagnosis, but can easily be ruled out with DIF. Oral manifestations, such as small blisters on the vermilion border of the lips, are seen in approximately 30% of cases. Epidermolysis bullosa acquista (EBA) appears to share a common antigen with BSLE and has been noted in patients with LE. The 2 conditions may represent variants of the same condition. EBA typically presents in a patient’s fourth or fifth decade of life, with acrally distributed mechanobullous lesions or widespread inflammatory vesicu-
lobuluous lesions appearing like bullous pemphigoid. EBA is more likely than BSLE to result in scarring. Furthermore, mechanical skin fragility is not a common feature of BSLE, though it is a feature of EBA. BSLE lesions generally last for many weeks to months, can undergo remissions and exacerbations, and respond favorably to treatment with dapsone. Conversely, EBA often lasts for many years and is frequently treatment resistant.

Some patients with LE and bullous lesions do not meet ACR criteria for either BSLE or EBA. Our patient had serologic evidence of connective tissue disease, as well as DIF findings typical for LE. Her clinical lesions and response to treatment were similar to that of BSLE. These findings suggest that her condition represents part of a spectrum of connective tissue disease-related bullous dermatosis.

The underlying pathophysiology of BSLE and EBA relates to the structure of the DEJ. Anchoring complexes, which are specialized focal attachment sites within the DEJ, are structurally weakened by the binding of autoantibodies to its components. The components of the anchoring complexes, which contain type VII collagen, react with the autoantibodies in BSLE, compromising the integrity of the DEJ. This may lead to the formation of subepidermal blisters.

The criteria for the diagnosis of BSLE proposed by Camisa and Sharma include a diagnosis of SLE, based on the criteria of the ACR, vesicles, and
bullae located on but not limited to sun-exposed skin; histopathologic findings similar to dermatitis herpetiformis; and deposition of IgG and/or IgM and often IgA at the basement membrane zone by DIF. Gammon and Briggaman\(^5\) classified BSLE into 2 distinct subtypes: patients with circulating antibodies to type VII collagen are designated as cases of BSLE-1, while patients designated as cases of BSLE-2 do not have these antibodies.

Some authors have suggested the current classification of BSLE be revised because some patients have autoantibodies bound to the epidermal side of 1 mol/L NaCl-split skin, which indicates involvement of DEJ components other than type VII collagen in BSLE.\(^2\)\(^,\)\(^8\) Patients also may test falsely negative for antibodies to type VII collagen, possibly because of degradation of the antibody during shipping or because they may possess antibodies to a different antigen. Failure to detect antibodies to type VII collagen does not rule out the possibility of BSLE, but data suggest that patients with lupus and bullous disease may represent a spectrum of related immunobullous disorders.

Histologically, the vesiculobullous eruption is typically characterized by dermal-epidermal separation with neutrophil-predominant inflammation in the upper dermis.\(^7\) In cases where the infiltrate concentrates in the dermal papillae as papillary microabscesses, the histologic picture is suggestive of dermatitis herpetiformis.\(^4\) Eosinophils also may be present, but are fewer in number. DIF studies characteristically show deposition of IgG, C3, IgA, and IgM at the DEJ in 2 types of patterns—granular and continuous granular—with an occasional mixed configuration.\(^4\) Circulating IgG antibodies to the DEJ have been detected in some, but not all, patients.

Ultrastructurally, electron microscopy localizes the blisters in the lamina densa region in most cases. Immunoelectron microscopic examination identified the deposition of the anti-DEJ antibodies on and beneath the lamina densa as in EBA, not in the lamina lucida as in bullous pemphigoid.\(^4\) These autoantibodies typically recognized the 290-kd and 145-kd antigens at the DEJ, with type VII collagen as the target. IgG autoantibodies to type VII collagen are believed to be pathogenic and contribute to the separation and blister formation both in BSLE and EBA.\(^4\) The production of these autoantibodies is regulated by the class II major histocompatibility complex.\(^4\)

Unlike patients with EBA, most patients with BSLE respond dramatically to dapsone.\(^5\) Although dapsone has both antibiotic and anti-inflammatory properties, the anti-inflammatory mechanisms mediate the therapeutic effect in BSLE. Dapsone

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**Figure 2.** Tense bullae on the lips (A) and ear (B).
directly impairs the myeloperoxidase-hydrogen peroxide-halide system of polymorphonuclear neutrophils (PMNs), which prevents generation of proinflammatory oxygen intermediates caused by activation of neutrophils. Inhibition of PMN chemotaxis and mitogen-stimulated transformation of lymphocytes is another mechanism by which dapsone interferes with inflammation. Furthermore, dapsone prevents cyclooxygenase-mediated production of prostaglandin E₂, further decreasing inflammation.

Patients with a glucose-6-phosphate dehydrogenase deficiency may experience severe hemolysis when taking dapsone; therefore, patients should be screened for this trait. Additionally, a baseline CBC and liver function test should be obtained and repeated weekly during the initial treatment period since dose-dependent hemolysis is the most
Bullous Eruption

common side effect of dapsone. Most patients will develop a 1- to 2-g drop in hemoglobin levels after initiation of treatment, which may be partially ameliorated by the concomitant use of 400 IU of vitamin E once a day. Other adverse reactions include methemoglobinemia, motor neuropathy, exfoliative dermatitis, hepatitis, headache, gastrointestinal upset, and rarely agranulocytosis. Dapsone also may induce a hypersensitivity syndrome with findings similar to those of infectious mononucleosis. The syndrome generally begins 4 to 6 weeks after initiation of treatment. Morbilliform eruptions with pruritus, fever, malaise, elevated erythrocyte sedimentation rate, lymphadenopathy, and lymphocytosis are common signs and symptoms associated with this syndrome. Immediate discontinuation of dapsone is recommended if symptoms arise. A good response to dapsone in the clearing of vesiculobullous lesions correlates with a better prognosis in BSLE; however, discontinuation of dapsone may allow new lesions to develop.

Colchicine is a therapeutic option for treatment of neutrophil-mediated bullous diseases. Colchicine is known to interfere with PMN chemotaxis and the release of lysozymal enzymes by PMNs. Our patient achieved resolution of lesions with 0.6 mg of colchicine 3 times a day. Administered in low doses, colchicine has relatively few side effects. The most common are transient diarrhea and abdominal discomfort; therefore, the dose requires titration to tolerance of these side effects. Other side effects of colchicine, such as neuropathy and bone marrow depression, are rare with low-dose therapy.

Bullous lesions in patients with LE often fail to respond to treatment with systemic corticosteroids alone, and long-term corticosteroid treatment is associated with adverse metabolic effects and bone demineralization. To limit corticosteroid toxicity, adjuvant therapy with azathioprine, antimarialars, and cyclophosphamide have been reported to be useful in cases unresponsive or intolerant to dapsone. Patients initiating steroid therapy should receive a baseline weight and blood pressure measures, as well as an ophthalmologic examination. Pretreatment laboratory studies should include tests for CBC, electrolyte count, calcium level, alkaline phosphatase level, creatinine level, human immunodeficiency virus, tuberculosis, and bone densitometry. Weight, blood pressure, and blood glucose should be followed monthly until a response is established. The side effects of prolonged therapy with systemic steroids include: psychiatric disorders, sleep disturbances, cataracts, gastrointestinal upset, weight gain, peptic ulcer disease, hypertension, atherosclerosis, infection, growth failure, suppression of the hypothalmic-pituitary-adrenal axis, secondary amenorrhea, hyperglycemia, glucose intolerance, inhibition of wound healing, subcutaneous atrophy, acne, hirsutism, osteoporosis, and aseptic necrosis of bone. The initiation of bisphosphonate therapy when corticosteroid therapy is begun will prevent a significant loss of bone mineral density. Bisphosphonate therapy also can improve bone mineral density in patients with established bone loss due to corticosteroid therapy.

Prystowsky et al reported successful use of azathioprine to treat BSLE. By metabolizing to 6-thioguanine, azathioprine is incorporated into DNA yielding strand breaks secondary to blockage of DNA synthesis. Because azathioprine is metabolized by thiopurine methyltransferase, patients should be screened for activity of this enzyme prior to initiation of therapy. Individuals who are homozygous for the allele conferring low activity of this enzyme (0.3%) are at risk for profound myelosuppression with azathioprine. More commonly, patients have high levels of the enzyme and are at risk for undertreatment of their disease with inadequate doses. Long-term risks of azathioprine therapy include an increased incidence of malignancy such as lymphoma, leukemia, and squamous cell carcinoma.

The prognosis in patients with SLE and bullous lesions is determined largely by the visceral manifestations of the SLE, yet the activity of the systemic and skin disease may not be linked. Our patient presented with immunobullous disease and serologic evidence of connective tissue disease. Her DIF finding was characteristic of LE. This case adds further evidence that there is a spectrum of related bullous disorders in patients with connective tissue disease.

REFERENCES


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