Extragenital bullous lichen sclerosus

Maxwell B. Sauder, MD, a Jaclyn Linzon-Smith, MD, b and Jennifer Beecker, MD, CCFP(EM), FRCPC a
Ottawa, Ontario, Canada

Lichen sclerosus is an inflammatory skin condition characterized by inflammation of the papillary dermis that leads to white scarlike plaques. It occurs classically in the genitals but also has extragenital manifestations with a variety of clinical presentations including a bullous variant. The purpose of this review is to characterize extragenital bullous lichen sclerosus, suggest that it may be more common than dermatologists realize, and discuss treatment of both routine and recalcitrant cases. (J Am Acad Dermatol 2014;71:981-4.)

Key words: bullous; cyclosporine; extragenital; lichen sclerosus; methotrexate; treatment.

Lichen sclerosus (LS) is an inflammatory skin condition characterized by white scarlike plaques. LS occurs classically in the genitals but also has extragenital manifestations. Scattered throughout the literature are “atypical” cases of bullous genital and extragenital LS.

Extragenital bullous LS is traditionally thought of as a rare variant of LS; however, no good epidemiologic studies have been done to support this idea. Given the number of case reports of extragenital bullous LS, the assumption that it is a rare variant may not be accurate. The purpose of this review is to characterize extragenital bullous LS and discuss a therapeutic ladder for this often difficult-to-treat disease.

EPIDEMIOLOGY

Classic genital LS is an uncommon disease with a prevalence difficult to estimate because of: (1) underreporting; (2) multiple names, including blurring of LS with morphea before 1940; (3) management by both dermatology and gynecology; and (4) asymptomatic presentations. A prevalence of 0.1% to 0.3% of patients was calculated by Wallace 1 in 1971. Studies have reported contradicting female: male ratios ranging from 10:1 to 1:1. In women, there is a bimodal distribution occurring prepubescently and postmenopausally. In men, the disease typically manifests in the fourth decade. 2

Extragenital involvement of LS has been estimated between 15% to 20% of all patients with LS. 3 However, to our knowledge, there have been no reports on the epidemiology of extragenital bullous LS. A literature search was performed using PubMed, yielding 26 reports with a total of 31 patients dating from 1936 to present. 4-29 A 32nd patient is reported in this review (see “Treatment” section). The female: male ratio was 7:2 with an average age of 62 years, similar to classic genital LS. More than half (18) of the reported cases were within the last 22 years from 1992 to present; the remaining 13 cases were reported in the preceding 56-year period (1936-1992). The low number of cases found in the literature, especially prior to 1992, is likely a result of the aforementioned difficulties in identifying the prevalence of LS. Although this literature review does not show any trend, the number of cases reported (31), especially during the last 22 years, might suggest that extragenital bullous LS is more common than dermatologists may realize.

PATHOGENESIS

The origin of genital LS is unknown. Theories include: genetic predisposition, autoimmunity, trauma, et.
infection, and hormonal abnormalities. Currently, autoimmunity in predisposed individuals is favored.

Several circulating antibodies have been found in a greater proportion of patients with LS than in control subjects. IgG antibodies against extracellular matrix 1 protein were shown in 74% of LS group serum versus 7% in control group serum. Extracellular matrix 1 protein helps to regulate the basement membrane zone (BMZ). In addition, several studies have demonstrated bullous pemphigoid antigen 180 and 230 (BP180 and BP230, respectively) antibodies against the BMZ in patients with LS; yet, the most recent study showed no statistical difference versus control subjects. Of relevance to bullous LS, all of the aforementioned antibodies target proteins within or regulating the BMZ. Similar to bullous pemphigoid, theoretically an autoimmune attack of these proteins could result in bullae formation.

**CLINICAL FEATURES**

Classic LS is characterized by ivory-white sclerotic atrophic plaques, most commonly in the anogenital region. Extragenital LS can occur anywhere on the body but favors the trunk (abdomen, chest, and back) and proximal extremities. Presenting symptoms are dryness and pruritus, but often extragenital LS can go unnoticed. Bullous LS may be both genital and extragenital, with flaccid bullae that may be hemorrhagic. The flaccid bullae lead to ulcerations and erosions that initially heal with significant postinflammatory erythema, and eventually obtain the characteristic ivory-white sclerotic plaques. A multitude of morphologic variants of LS have been reported including bullous LS (Table I).

**PATHOLOGY**

Early in the disease course, LS shows a lymphocytic vacuolar interface dermatitis with epidermal atrophy and orthohyperkeratosis. The most characteristic changes are edematous homogenization of the collagen and a loss of elastic fibers in the papillary dermis eventually leading to hyalinization and sclerosis of the papillary dermis.

Histologically, bullae formation (Fig 1) has been explained through 2 mechanisms. Firstly, the vacuolar dermatitis can lead to liquefaction degeneration of the basal layer disrupting the stability of the BMZ. Secondly, edema of the papillary dermis disrupts the collagen fibers supporting the superficial capillaries and flattens the rete ridges. This weakened state coupled with epidermal atrophy may allow for blister formation with minimal trauma or sheering forces from regular movement.

**TREATMENT**

The treatment of extragenital bullous LS is similar to that of genital LS (Table II).

**First-line therapies**

Recommended first-line therapies include super-potent topical corticosteroids with or without maintenance topical calcineurin inhibitors, intralesional corticosteroids, or oral corticosteroids. Based on the reported cases of extragenital bullous LS, the most common treatment is the application of topical corticosteroids, a relatively safe and inexpensive modality.

The majority of cases used topical clobetasol propionate 0.05%, a class-I super-potent steroid, once or twice daily with or without occlusion. Symptomatic response can be achieved within days to weeks; however, extragenital LS often does not respond as well as classic LS. In 1 case, topical clobetasol was used initially for 2 weeks to achieve control followed by long-term daily use of pimecrolimus cream to ensure remission. In limited disease, intralesional corticosteroids at anti-inflammatory doses (triamcinolone acetonide <10 mg/mL) may be used.

Systemic steroids have been used with similar effects to topicals. Because of the side effects of systemic corticosteroids, their use should be limited to widespread disease where topical application would be challenging, or cases refractory to topical treatment.

Three reported cases used systemic antibiotics because of presumed secondary infections or the belief that extragenital bullous LS is a reaction to *Borrelia burgdorferi*. As extragenital bullous LS likely does not have an infectious cause, the use of antibiotics is recommended only if a secondary infection is present but not for primary disease management.

**Second-line therapies**

For patients who do not achieve adequate clinical control with corticosteroids, methotrexate or phototherapy may be used.
To illustrate the effectiveness of methotrexate, the authors present a case of a 69-year-old woman with widespread biopsy-confirmed extragenital bullous LS. The patient failed to respond to super-potent topical steroids and had complications secondary to prednisone and acitretin including elevated transaminases, gamma-glutamyltransferase, and alkaline phosphatase. She was transitioned to methotrexate starting at 5 mg weekly tapering the prednisone. Clinical response was seen within weeks and her liver enzymes normalized within months. The patient remains on methotrexate and in remission.

Although methotrexate is commonly used in morphea, a literature review found only 2 studies with a total of 8 patients with LS treated with methotrexate. All 8 of the cases had extragenital involvement, but only 1 with bullae. All cases responded with a clinically significant reduction in severity or clearing and were bridged with either systemic or topical steroids. In follow-up at least 3 months posttreatment, the average response was a 75% reduction of area involved. The case described by the authors is the second reported case of extragenital bullous LS treated with methotrexate and demonstrated complete disease control. For difficult cases of extragenital bullous LS or extragenital LS, methotrexate may be considered when first-line therapies have failed or produced adverse drug events, or there is extensive debilitating involvement.

There are case reports and series of the use of ultraviolet (UV)A, psoralen plus UVA, and narrowband UVB in the treatment of extragenital LS. UVA1 is most frequently associated with significant clinical improvement. One study concluded that the extragenital lesions cleared more effectively than the genital lesions. Psoralen plus UVA has been reported to reduce pruritus and lesions, leaving only minimal scarring in extragenital LS. One case of narrowband UVB reported resolution of clinical lesions within 3 months. There are no reported cases of extragenital bullous LS treated with phototherapy. Further studies are required to determine if phototherapy may be a useful modality.

**Third-line therapies**

Acitretin has been reported as treatment in cases of genital LS that included ulcerations and erosions. In a double-blind placebo-controlled study measuring clinical response, 14 of the 22 patients receiving acitretin (20-30 mg/d) for 16 weeks responded versus 6 of the 24 patients in the placebo-controlled group.

The lymphocytic inflammatory infiltrate of LS theoretically suggests that an immunomodulator might be effective. Cyclosporine can be used to achieve acute disease control while transitioning to a maintenance treatment. One study of 5 patients with recalcitrant genital LS were treated for 3 months with cyclosporine at an initial dose of 3 to 4 mg/kg/d and decreased to 1 mg/kg/d. All patients demonstrated subjective improvement beginning in the first month with only mild adverse drug events.

**Conclusion and recommendations**

In conclusion, extragenital bullous LS may be more common than dermatologists realize. The
treatment of this disease entity is similar to genital LS with potent topical corticosteroids being first-line therapy. For those patients not responsive to topical steroids, the authors report a case of remission using methotrexate bridged with oral steroids, but phototherapy, acitretin, and cyclosporine may be other useful therapies.

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REFERENCES