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AN OVERVIEW OF LICHEN SCLEROSUS

INTRODUCTION

Lichen sclerosus (LS) is a chronic, inflammatory disease that typically affects the genital skin, and less frequently on other skin sites. It is characterized by white, shiny, scar-like atrophy. Symptoms include pruritus, burning, progressive atrophy, and in severe cases, loss of normal genital architecture, and functional impairment.

Synonyms: kraurosis vulvae, balanitis xerotic obliterans (in males), lichen sclerosus et atrophicus

EPIDEMIOLOGY

The exact incidence and prevalence of lichen sclerosus are not known due to a lack of population-based data in the literature. One previous review of a general gynecology practice estimated the prevalence of vulvar LS to be around 1.7%[1] and a Dutch cohort study estimated the incidence rate of lichen sclerosus to range from 7.4 to 14.6 per 100,000 woman-years between 1991 and 2011.[2] Peak incidence occurs in postmenopausal women, with a second peak in prepubertal girls, followed by men in their fourth decade.[3]

ETIOLOGY/PATHOGENESIS

The cause of LS remains unknown. Several HLA haplotypes have been associated with the disease and identified in the peer-reviewed literature.
(HLA-DQ3, HLA-DQ7, HLA-DRB1*12, HLA-DRB1*0301/04/DQB1*0201/02/03, among others).[4-6] Autoantibodies against extracellular matrix protein 1 (ECM-1) have also been identified in LS patients. Indeed, autoimmunity is believed to play a primary role in the disease, and several autoimmune comorbid conditions have been associated with LS, including autoimmune thyroiditis, alopecia areata, vitiligo, pernicious anemia, celiac disease, and morphea.[7,8] *Borrelia burgdorferi sensu lato* species has also been implicated in the pathogenesis of lichen sclerosus, with one study detecting *Borrelia* species in 63% (38 of 60 cases) of lichen

sclerosus tissue specimens.[9] Other triggers, such as influenza vaccination[10], surgery[11] , and genital piercing[12] have been described as well in the form of single case reports.

CLINICAL FEATURES

LS can affect both the genital and extragenital skin. The classic morphology is characterized by ivory white, porcelain-like, sclerotic, atrophic papules and plaques. These lesions may also have telangiectasias, follicular plugging, erosions, purpura, and haemorrhagic bullae. In the anogenital region in women, a "figure-of-eight" configuration has been described, with circumferential lesions involving the vulva, perineum and anus. In advanced cases, the normal architecture of the labia minora, labia majora, and clitoral hood may be resorbed, resulting in narrowing of the vaginal introitus. In men, lesions may similarly present as sclerotic, shiny, white lesions, often on the glans penis and inner aspect of the foreskin. Constriction, phimosis, paraphimosis, and recurrent balanitis are complications of LS in men. In advanced stages, patients may also have urinary obstruction. Patients with LS, both men and women, often have significant dyspareunia, pruritus, dysuria, and general soreness and discomfort.

Because of the chronic inflammatory state of LS, there is a risk of malignancy in longstanding lesions. The 10-year vulvar squamous cell carcinoma incidence in women with lichen sclerosus was associated with concurrent vulvar intraepithelial neoplasia and age at time of lichen sclerosus diagnosis (5.9% in women of ≥70 years, 3% in women between 50 and 70 years, and 1.8% in women <50 years).[2]

DIFFERENTIAL DIAGNOSIS

Lichen sclerosus must be delineated from a variety of other diseases of the anogenital region, including morphea, erosive lichen planus, and graft vs host disease. In men, Erythroplasia of Queyrat, balanitis, and extramammary Paget's must all be considered. In young children, it is important to rule out sexual abuse.[3,13,14]

PATHOLOGY

Biopsies of lichen sclerosus will typically show a thinned epidermis and a lichenoid interface dermatitis characterized by vacuolar degeneration of the basal layer and a band-like lymphocytic infiltrate.[13-16] Macrophages and mast cells can also sometimes be seen in the infiltrate. Follicular plugging may be seen and rete ridges may be flattened. Below this, in the dermal level, lesions may demonstrate homogenized dermal collagen and edema. The key differentiating feature between lichen sclerosus and morphea is the loss of elastic fibers, which is seen in LS but not morphea.[14-16]

TREATMENT

The current standard of care for LS patients is a high potency topical steroid such as clobetasol propionate 0.05% daily or alternating with a non-steroidal topical or rest period.[3,14,17] For recalcitrant cases, or for patients unable to apply topical steroids, intralesional steroid injections can be helpful.[17] The most commonly used non-steroidal alternatives are tacrolimus and pimecrolimus. One study of sixteen patients (10 with anogenital and six with extragenital localization) were treated with topical tacrolimus ointment twice daily. Results demonstrated improvement in a majority of genital LS patients[18], but none in patients with extra-genital LS.

No adverse effects were observed in this study. Due to a black box warning regarding lymphoma risk associated with tacrolimus and the risk of squamous cell carcinoma (SCC) arising in LS, clinicians should consider counselling patients about this theoretical risk However, no studies have shown development of SCC as a result of topical calcineurin inhibitors in patients with LS.

Although topical estrogen and progesterone preparations have been used for post-menopausal dryness and dyspareunia, there is no evidence to support the use of such preparations in LS.[17] Topical testosterone is also not recommended and has been shown to be inferior to clobetasol.[17] Furthermore, studies have demonstrated unacceptable adverse effects of topical testosterone including clitoral hypertrophy, hirsutism, acne, and menstrual abnormalities.[17,19,20]

Phototherapy has long been considered in the treatment of LS. The most evidence exists for the use of PUVA/UVA1, but the data is limited to a few case series, and patients should be warned about risk of carcinoma with PUVA.

The use of systemic treatments such as prednisone, cyclosporine, and methotrexate have been elucidated through case reports in the literature. The largest study of methotrexate was a retrospective review of 28 patients who had previously failed topical therapies. The authors found improvement in 75% of patients who received weekly doses of methotrexate ranging from 2.5 mg to 17.5 mg (median= 10 mg), however several patients had to discontinue methotrexate due to side effects.[21]

There are conflicting case reports involving the use of hydroxychloroquine and thus a recent review of treatment strategies for LS[17] did not recommend this medication.

There is some evidence for the use of systemic retinoids in LS. One randomized controlled trial[22] found a significantly higher number of responders in patients receiving 35 mg of acitretin daily (14 of 22 patients), compared with the placebo group (6 of 24 patients). Another randomized, double-blind, placebo controlled trial done in males with LS[23] also found some positive effect of acitretin. In this study of 49 completers who were eligible for statistical analysis, complete response was achieved by 36.4% (12 of 33) of the acitretin group vs 6.3% (1 of 16) of the controls, while 36.4% (12 of 33) vs 12.5% (2 of 16) achieved partial resolution, respectively.

A potential hypothesis for the treatment of LS centers on the use of systemic antibiotics, which links back to the theory that *Borrelia* species may trigger LS. One retrospective study of 15 men and women with steroid-resistant LS were treated with one of: intramuscular penicillin and oral penicillin, intramuscular cephalosporin, oral penicillin, or oral cephalosporin.[24] The authors noted that all patients showed significant response within a few weeks, particularly those who had received intramuscular antibiotics, with significant reduction in pain, pruritus, and burning. Though not a first-line treatment approach, clinicians may consider the use of intramuscular ceftriaxone 1 gram every two weeks for three doses, then once a month on a PRN basis; or intramuscular penicillin G benzathine suspension dosed at 2.4 million units every 2 weeks for three doses, then once a month on a PRN basis in resistant LS cases.[17]

Newer, investigative treatments include the use of fractional carbon dioxide laser (i.e. MonaLisa Touch®) which is currently being investigated at Sunnybrook Health Sciences Centre. The published data on this treatment modality is limited, with mostly case reports reported in the literature.[25-28] The largest published study of forty women with LS who failed clobetasol propionate demonstrated improvement in vulvar itching, dryness, sensitivity during intercourse and dyspareunia. Itching relief was noted after only one treatment in several patients.[29] No systemic or local adverse reactions were reported in this study. Fractional CO2 laser has also been studied in males, with improvement noted in DLQI scores, symptoms of LS, sexual function, and no relapse at the 6-month follow-up mark.[30] This study also reported that the fractional laser was well-tolerated, with no significant adverse effects. Some patients experienced edema, short duration of burning, and erythema, all of which resolved within hours to days.

Surgical interventions have also been studied in LS. In men, surgical intervention such as circumcision can often be curative in mild-to-moderate cases.[13,17] In women with advanced LS, perineotomy and lysis of adhesions can provide symptomatic relief.[17] Platelet-rich plasma has also been studied in a non-randomized setting, with excellent response rates in subjects ranging from 62%-100%.[31-35]

SUMMARY

Lichen sclerosus is a chronic, inflammatory disease that primarily affects the anogenital area in both men and women. Treatment is essential to prevent progression of the disease, which can lead to permanent deformity and decreased quality of life. The mainstay of treatment includes potent topical steroids and in some cases, surgery can be curative. In cases unresponsive to topical steroids, systemic treatments such as systemic retinoids, methotrexate, and antibiotics may be utilized. Fractional laser and platelet-rich plasma are promising new treatments and may be considered in recalcitrant cases.

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