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PRACTICAL DERMATOLOGY

Lichen Sclerosus

V. Monsálvez,* R. Rivera, and F. Vanaclocha

Servicio de Dermatología, Hospital 12 de Octubre, Madrid, Spain

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Review

Abstract
Lichen sclerosus is a chronic inflammatory mucocutaneous disease that is highly bothersome for men and women of all ages. The exact etiology is unknown, although genetic and autoimmune factors, as well as infections, have been implicated in its pathogenesis. Firstline treatment is highly potent topical corticosteroid therapy for short periods. Surgery is reserved for cases of phimosis, urethral stenosis, synechiae, and squamous cell carcinoma.

PALABRAS CLAVE
liquen escleroso;
liquen escleroso y atrófico;
revisión

Liquen escleroso

Resumen
El liquen escleroso es una enfermedad inflamatoria crónica mucocutánea que causa una gran molestia en hombres y mujeres de todas las edades. La etiología exacta es desconocida, aunque factores genéticos, autoinmunitarios e infecciosos se han implicado en su patogénesis. El tratamiento de primera línea es la corticoterapia ultrapotente tópica durante un tiempo limitado, y se reserva la cirugía en caso de fimosis, estenosis uretral, sinequias y carcinoma escamoso.

Lichen Sclerosus

Lichen sclerosus (LS) is a chronic skin disease, with special preference for the genital area, although it can appear on any region of the body. Hallopeau[1] described it for the first time in 1887, and considered it an atrophic form of lichen planus, and in 1892 Darier[2] named it lichen planus sclerosus. This disease has been known as kraurosis vulvae, balanitis xerotica obliterans, leukoplakia, and lichen sclerosus et atrophicus. However, in 1976, the International Society for the Study of Vulvovaginal Disease proposed the name of lichen sclerosus to unify all the previous terms.

*Corresponding author.
E-mail address: monsalvezhonrubia@hotmail.com (V. Monsálvez).

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Epidemiology

The exact prevalence of this disease is difficult to calculate, because it is managed by several different specialties (gynecology, dermatology, urology, and pediatrics). In 1971, Wallace estimated its incidence between 1/300 and 1/1000 patients attending dermatology clinics.[3] Lichen sclerosus has been reported in all age groups and both sexes, although it preferentially affects 40- to 60-year-old women at a ratio of 10/1.[4] In girls, its incidence is estimated to be 1/900[5] (7%-15% of all cases occur in prepubertal girls[6]). In men, the disease usually begins in the third decade of life, and in boys histological findings are common in circumcision samples (40% in a prospective study of 1178 patients[7]). Caucasians are the group most affected, although cases have been reported in other ethnic groups.[6,8]

Clinical Features

The presentation of LS is usually similar in both sexes, with the appearance of erythematous papules that coalesce initially into erythematous plaques and then become white and hard. In women, the most frequent location is usually the anoperineal region, forming a typical figure-8 pattern around the labia minora and anus, without affecting the vagina or hymen (Figure 1 and Figure 2). It usually presents with pruritus, dysuria, dyspareunia, or pain on defecation, the most frequent symptom in girls and a cause of constipation.[9] If the inflammatory process is intense and long-lasting, atrophy, retraction of the vulva, and synechiae of the labia minora that alter the structure of the external genitalia may occur.[4]

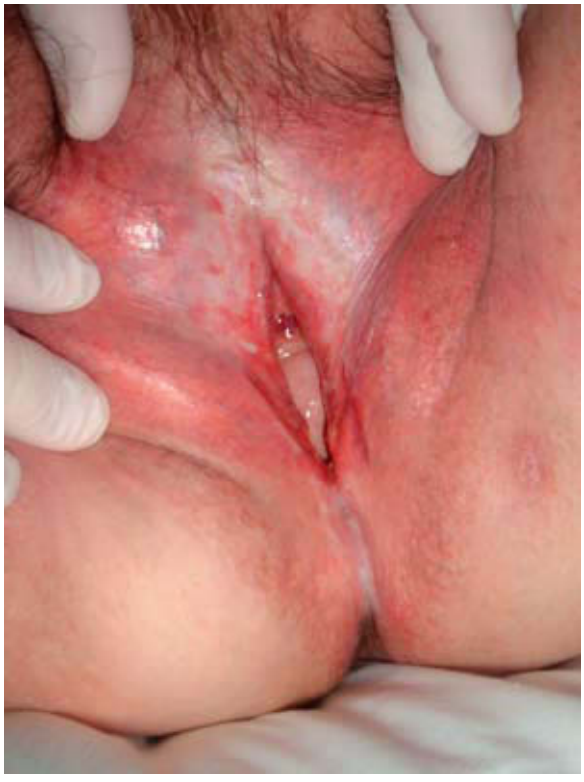

Figure 1 Lichen sclerosus in a 50-year-old woman. Atrophic white plaques in a figure-8 pattern.

Figure 2 Lichen sclerosus in a 6-year-old girl. Typical figure-8 pattern with perineal fissure.

In men, anal involvement is rare, and the disease is usually limited to the glans penis and prepuce. This may lead to difficulties in retraction and pain during erection (a retrospective study of 522 patients reported that the glans penis and prepuce were affected in 57%, the meatus in 4% and the urethra in 20%).[6] Symptoms usually begin as in women, with erythematous papules that turn white and then progress to an atrophic band that can lead to phimosis, paraphimosis, and urethral stenosis[4] (Figure 3).

A form of LS known as perianal pyramidal protrusion has been reported in children. This is an exophytic lesion that develops in the perianal region and presents histological signs compatible with LS.[10-12]

Extragenital involvement occurs in 15% to 20% of the patients, with plaques that resemble plaque morphea and that are usually asymptomatic. They may be located on any part of the body (most often on the upper back, neck and abdomen)[4,6,8] (Figure 4 and Figure 5). The oral mucosa is rarely affected, with few cases reported in the medical literature. It usually presents as asymptomatic white plaques that affect the oral mucosa and labial mucosa.[13]

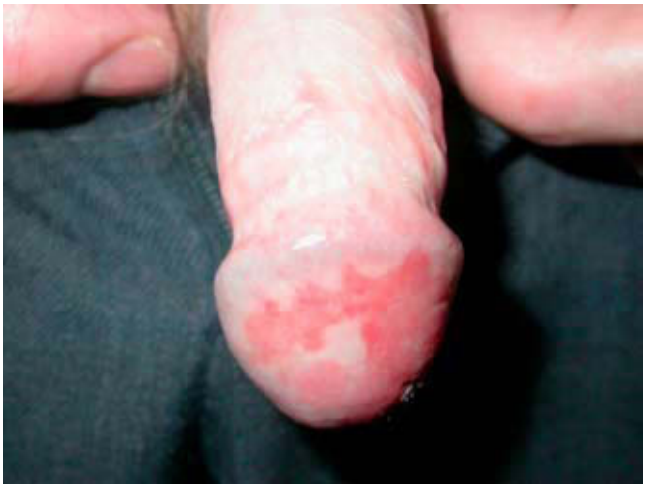

Figure 3 Lichen sclerosus in a 40-year-old man. Shiny erythematous plaques without infiltrates on the glans penis.

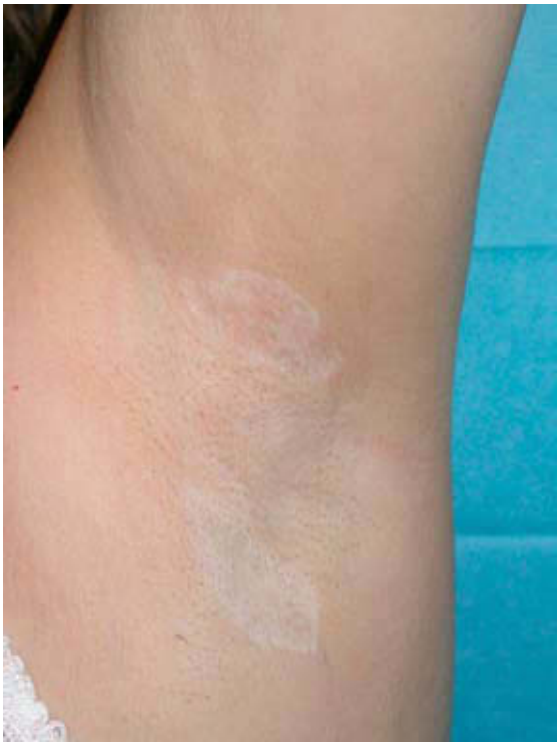

Figure 4 Extragenital lichen sclerosus in the axillary region. Nacreous white plaque without hair follicle involvement.

A case of LS has been reported that involved most of the trunk and scalp with the formation of nonhemorrhagic bullae that subsequently resolved to leave scarring alopecia.[14]

Etiology

Several factors have been associated with the onset of LS (Table 1).

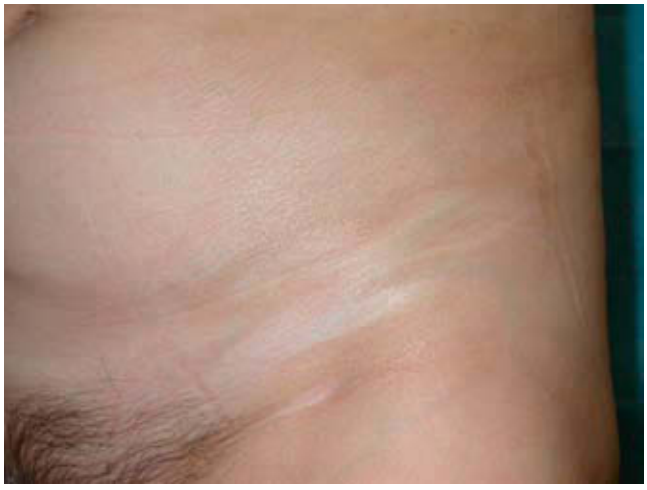

Figure 5 Extragenital lichen sclerosus on the right groin.

Table 1 Pathogenic Factors

• Autoimmune factors
• Genetic factors
• Hormonal factors
• Infections
• Trauma

Autoimmune Factors

Arguments supporting the hypothesis that LS is an autoimmune disease include, on the one hand, the greater prevalence of autoimmune diseases reported in patients with LS and, on the other hand, the presence of autoantibodies and a family history of immune disease.

Powell et al[15] demonstrated a greater number of cases of autoimmune thyroid disease and vitiligo in girls with LS. Prior to this, Wallace,[3] Goolamali et al,[16] Harrington and Dunsmore,[17] Marren et al,[18] and Meyrick et al,[19] among others, reported a greater number of autoimmune diseases in women with LS compared to the general population. Similarly, cases have been reported in the medical literature of men with LS presenting autoimmune conditions.[20,21]

Recently, extracellular matrix protein 1 has been suggested as a possible LS antigen, and the presence of immunoglobulin G autoantibodies was demonstrated in 67% of the patients with LS compared to the control group in which 7% of serum samples were positive.[22]

Genetic Factors

Genetic factors have been proposed as underlying the development of LS based on the presence of the disease in several family members,[23] in identical twins[24] (who share all their genes) and in nonidentical twins.[25] Various studies have demonstrated that patients with HLA-DQ7[15] are at higher risk of presenting LS. Interleukin 1 receptor antagonist gene polymorphism has also been associated with the severity of LS.[26]

Hormonal Factors

Sex hormones are considered to be an influential factor in the development of LS. On the one hand, peak incidence coincides with decreased estrogen levels, such as during premenarche and menopause, and thus a relevant role has been attributed to estrogens in the development of LS.[4,5,8] Decreased levels of testosterone, androstenedione, and dihydrotestosterone in patients with LS have also been observed.[27] Despite this, treatment with estrogens and testosterone has not demonstrated clear benefit in these patients.

Infection

Several microorganisms have been associated with the appearance LS lesions:

- *Borrelia burgdorferi*: although attempts have been made to isolate DNA in histological samples of LS, it could not be detected in a recent study of patients with LS.[28]
- Hepatitis C virus.[29]
- Human papillomavirus: this has been demonstrated using in situ hybridization and immunohistochemical study in samples taken from patients with LS.[30] The role of the virus in the development of carcinoma on previous LS lesions has been a topic of debate.[31-33]

Koebner Phenomenon

In LS, as in other skin diseases, lesions are more often found in areas that have undergone trauma. Cases of LS have been reported following sunburn and radiation therapy, and after surgery, as occurs around vulvectomy scars.[4,6]

Other Factors

- Psoriasis: recent studies have hypothesized an association between LS and psoriasis (psoriasis is present in 7.5% of the patients with LS compared to 1.6% in the general population).[34,35]
- Diabetes: a statistically significant association between patients with LS and diabetes has been reported.[36]

Histology

Histological findings of LS depend on the phase of the disease at the time of biopsy. Typical cases present hyperkeratotic epithelium (if the patient tends to scratch) or atrophic epithelium, with hydropic degeneration of the basal layer or mild spongiosis, with subepithelial sclerotic collagen and lymphocytic infiltrate in the dermis. The arteries and arterioles of the mid and upper dermis present signs of endarteritis obliterans.[4,37] Immunohistochemical study is positive for antibodies against collagen I, collagen III, and elastin[38] (Figure 6).

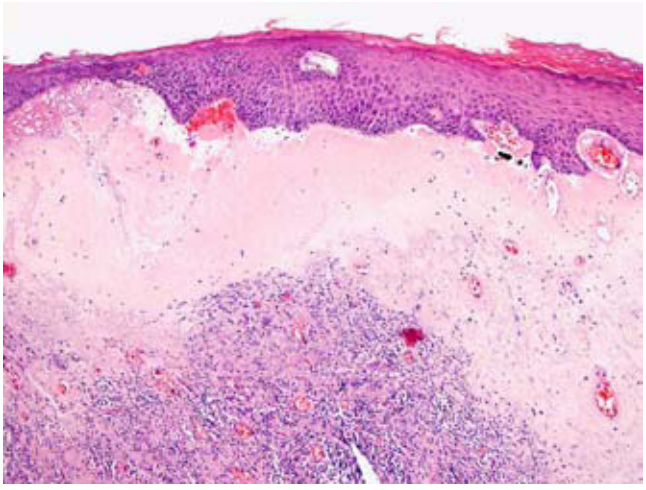

Figure 6 Hematoxylin-eosin staining ×20. Sclerotic collagen bundles in the form of band in the superficial dermis with lymphoid infiltrate in the area of the deep dermis. Epidermis with mild parakeratotic hyperkeratosis.

Complications

Long-standing lichen sclerosus can present several complications (Table 2):

Table 2 Complications

Synechiae
• Labia majora
• Phimosis
• Paraphimosis
• Urethral stenosis
Infections
Epidermoid carcinoma
Sexual problems
Constipation

- Synechiae: these particularly affect the labia minora, forming adhesions that may surround the clitoris and lead to phimosis. In men, these adhesions cause phimosis and paraphimosis of the prepuce, and may also lead to urethral stenosis if this region is affected by LS.[4,6,8]
- Infections: these result from scratching and manipulation of the affected region.[6,8]
- Epidermoid carcinoma: in women, the risk of malignancy is 4% to 6%,[8,39] whereas recent studies have shown this to be around 8% in men,[40] although previous studies reported lower risk.[8] Malignancies have not been reported in extragenital regions.[4]
- Sexual problems: dyspareunia, vulvodynia, and decreased libido.[41]
- Constipation: this is usually a complication found in untreated children arising from discomfort on defecation.[42,43]

Differential Diagnosis

The differential diagnosis should address disease entities that can be located in the genital area and that present white or erythematous plaques, with erosions or that leave hypopigmentation[4]:

- erosive vulval lichen planus or atrophic forms
- vitiligo
- postinflammatory hypopigmentation
- morphea
- lichenification
- postmenopausal atrophy
- cicatricial pemphigoid
- atrophic candidal vulvitis
- leukoplakias
- genital herpes simplex

In children, the differential diagnosis should take into account lesions resulting from sexual abuse, since these can present as erosions, fissures, hematomas, bleeding, and secondary scars in the anogenital area. Several articles report that in certain cases there is an association between LS and previous sexual abuse (Koebner phenomenon).[41-44] According to Powell and Wojnarowska,[45] in up to 70% of 72 cases of LS the first diagnosis was sexual abuse, as in the case of the 6-year-old girl reported by Isaac et al.[46] An initial diagnosis of sexual abuse was made in view of the presenting lesions in the perianal region. After multiple serological and histological studies, and interviews with psychiatrists and psychologists, LS was diagnosed with severe pruritus. The scratching caused by this led to erosions and fissures reminiscent of lesions present in sexually abused children. In the case reported, it was confirmed that her hymen and anal sphincter tone were intact, unlike cases of sexual abuse. Nevertheless, the diagnoses are not mutually exclusive and can coexist, as shown by Warrington and De San Lázaro[47] in a review of 42 patients, 29% of whom presented signs of sexual abuse and LE.

Treatment

If a patient has suspected LS, a complete medical history should be taken and any personal and family background of immune disease thoroughly explored (vitiligo, symptoms of diabetes, thyroid disease symptoms, alopecia areata, or digestive symptoms).

Physical examination should rule out extragenital involvement, including involvement of the oral mucosa. Signs of active disease should be noted: erosions, petekias, hemorrhages, and surface hyperkeratosis.

Definitive diagnosis is obtained by biopsy, and samples are taken from regions where malignancy is suspected; it is essential to rule out the coexistence of epidermoid carcinoma.

Complementary studies should include complete blood count, biochemical study (with glucose), antibodies for the systematic detection of concomitant autoimmune disease (antinuclear antibodies, antithyroid antibodies, antiparietal cell antibodies, and antimicrosomal antibodies), and thyroid hormones.[48]

The treatment goals are to reduce irritation, burning sensations and pain, heal the cutaneous lesions, minimize scarring, and prevent malignization. Before beginning pharmacological treatment, basic hygiene measures should be recommended: neutral soap should be used, irritants avoided, and cotton underwear used although this should be worn as little possible, especially at night. Emollients and lubricants should be used if needed and any infections caused by these should be detected and treated. Topical estrogens are useful in the case of vaginal atrophy, but not for LS itself.[4] The pharmacological treatment of choice in LS is highly potent topical corticosteroids (level of evidence IA [Table 3]), such as 0.05% clobetasol propionate, in children and in adults. Treatment should begin with 1 or 2 applications per day for 4 weeks, continue with 1 application every 48 hours for another 4 weeks and, subsequently, 2 or 3 applications per week for 1 month more.[6,8,48] A checkup is recommended after 3 months of treatment, and if symptoms of activity persist, topical corticosteroids should be maintained (2 or 3 applications per week) or be replaced by topical 0.1% tacrolimus (level of recommendation B, level of evidence II-i) or topical 1% pimecrolimus (level of recommendation C) 3 times per week.[49-52]

If the patient does not tolerate or respond to topical corticosteroids, the possibility of allergy to these should be investigated, since this may be the cause of treatment failure.[53] It should be emphasized that no more than 1 30 g tube of clobetasol propionate should be used during the 3 months of initial treatment, and no more than two-thirds of a tube should be used in children.[6]

Other treatments for LS have been used, but none has proven to be more effective than topical corticosteroids in clinical trials. Topical 2% testosterone[54] (level of recommendation C, level of evidence IV), despite being more effective than placebo, is not superior to corticosteroids in the treatment of LS. The use of topical 0.005% calcipotriol[55] applied daily for 1 week (level of evidence II-iii) increasing to 2 daily applications for several months will alleviate the pruritus. Other treatments, such as carbon dioxide laser therapy[56-58] (level of recommendation D), cryosurgery[59] (level of recommendation C, level of evidence III), photodynamic therapy[60] (level of recommendation C, level of evidence III) and phototherapy (ultraviolet A1[61] and psoralen with ultraviolet A[62]; level of recommendation

Table 3 Levels of Evidence

Level of Recommendation
A. Good evidence for the use of the procedure
B. Some evidence for the use of the procedure
C. Little evidence for the use of the procedure
D. Little evidence for rejecting the use of the procedure
E. A great deal of evidence for rejecting the use of the procedure
Levels of Evidence
I. Randomized controlled studies
II-i. Nonrandomized controlled studies.
II-ii. Case-control studies or cohort studies
II-iii. Case series
III. Expert opinion
IV. Insufficient evidence due to methodological problems

D), lead to improvements in symptomatology, although the lesions persist, and require many treatment sessions without achieving good cosmetic results. In patients resistant to topical treatment, oral retinoids can be used with good long-term results (level of recommendation C, level of evidence I), although with consequent adverse effects.[63,64] There are anecdotal reports of cases treated with stanozolol, *para*-aminobenzoic acid, hydroxychloroquine, and hydroxycarbamide.[65]

In addition to dermatological treatment, concomitant therapy with antidepressants may be needed to alleviate the anxiety caused by this disease, and to relieve subjective symptomatology.

Surgery is reserved for the majority of the complications. Adhesions and vulval synechiae should be treated by genital reconstruction, despite the risk of recurrence. In men, circumcision is the treatment of choice for lesions that cause phimosis, and urethral dilatation in cases of urethral stenosis. In all cases complicated by carcinoma, surgery is the treatment of choice.[4,6,8]

All patients with LS symptoms should be treated due to the risk of malignancy and to improve the quality of life. The situation is less clear in asymptomatic patients and in children. Some authors suggest that each case should be considered on its own merits and the advantages and disadvantages assessed, since corticosteroid treatment involves several risks, but these should be balanced against the risk of developing carcinoma.[39,48]

Prognosis

Although LS is a chronic disease and patients should be made aware of the possibility of insidious progression,

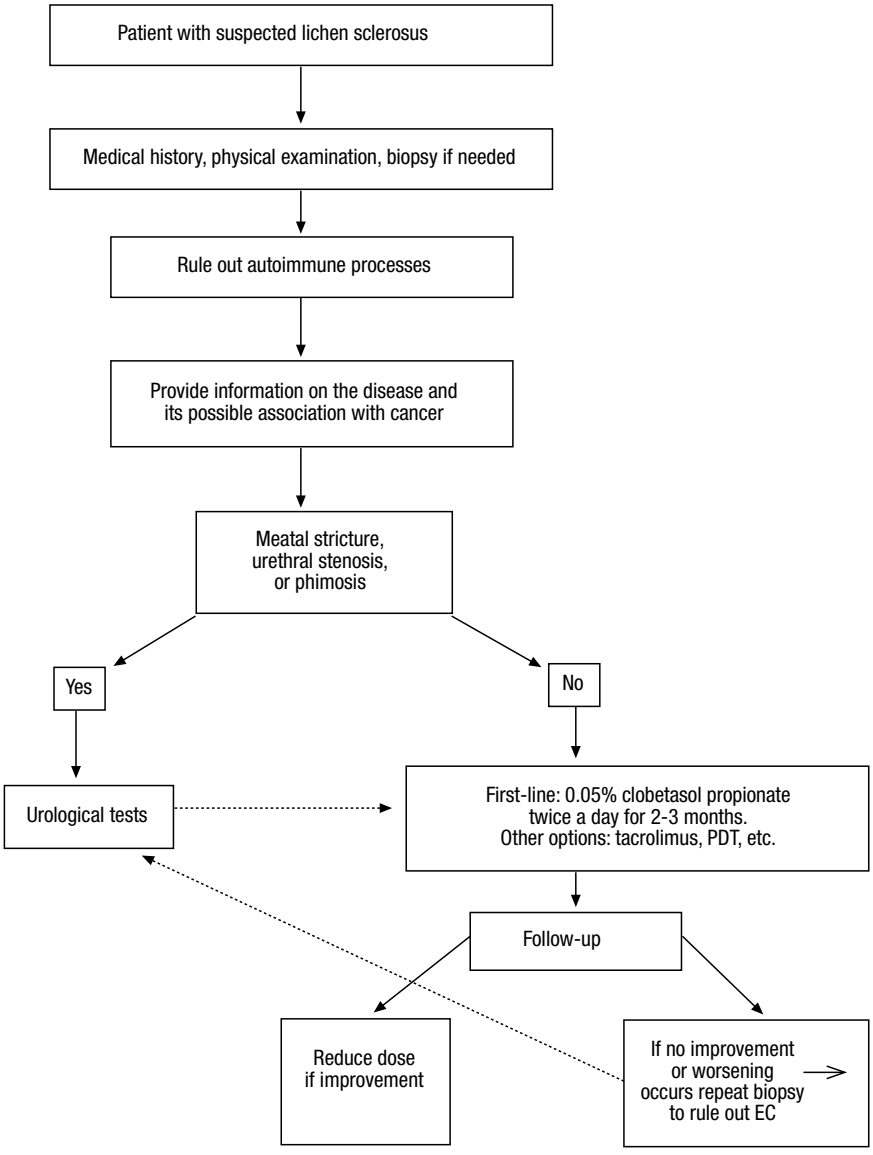

Figure 7 Treatment of lichen sclerosus. EC indicates epidermoid carcinoma; PDT, photodynamic therapy (adapted from Pugliese et al[6]).

spontaneous resolution has been reported, especially in girls coming into puberty.[4,6,8,39,48]

Conclusion

Lichen sclerosus is a chronic inflammatory disease that can affect any age group and both sexes and whose symptoms have a negative impact on the quality of life of the patient. First-line treatment is topical 0.05% clobetasol propionate. The patients should be monitored due to the risk of developing epidermoid carcinoma. We present an algorithm that may be useful in the treatment of this disease (Figure 7).

Conflicts of Interest

The authors declare no conflicts of interest.

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