Case report

Lichen sclerosus: a review of literature and a case of an atypic surgical treatment

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Abstract. Lichen sclerosus is a chronic immuno-mediated skin disease of the genital region in men and women. The treatment may be pharmacological or surgical, the choice depending on the extension of the involved area, the histological pattern and the level of functional disease complained by the patient. If the biopsy is negative for neoplastic degeneration the treatment may be pharmacological only. In our paper, we describe the case of a patient with vulvar disease and labial fusion, burial of the clitoris and severe introital stenosis. In this case, the treatment was surgical. (www.actabiomedica.it)

Key words: Lichen sclerosus, Vulvar disease

Introduction

Lichen Sclerosus (LS), previously referred to as balanitis sclerotica obliterans (BSO) in men and chronic atrophic vulvitis in women, was first clinically described in 1887 by Hallopeau, who gave it the name lichen plan atrophique; later, in 1892, Darier described the histological feature of the lesion and named the disease lichen plan sclérux (1).

Lichen sclerosus is a chronic immuno-mediated skin disease of the genital region in men and women. Although any skin site may be affected, the most common is the anogenital area and, more rarely, the oral mucosa. An important relationship between lichen sclerosus and vulvar squamous cancer has been demonstrated: this is the reason why a precocious diagnosis and a correct management of the disease is fundamental. The treatment may be pharmacological or surgical, the choice depending on the extension of the involved area, the histological pattern and the level of functional disease complained by the patient. In the text below, we deal with the state-of-art about epidemiology, aetiology, pathogenesis, diagnosis and management (both pharmacological and surgical).

Epidemiology

Lichen sclerosus preferentially occurs in female between 40 and 60 but it is also common in children under 2 years old (2). Both in women and in children an association with atopy is reported, too (3, 4). With regard to the major prevalence in female sex, some investigators reported a prevalence of ten to one compared with male sex (5, 6). Noteworthy, it seems more common in Caucasians (6). It is not known the exact prevalence of lichen sclerosus, because some patients may refer no symptoms, and some other may be embarrassed asking help to a physician. Moreover, patients may be visited by different specialists, such as dermatologists, urologists, gynaecologists and surgeons.

Lichen sclerosus frequently affects the anogenital area (85-98% of cases) (2, 7), sometimes presenting with a figure-of-eight pattern around the vulva and the anus. In a minority of cases it affects other skin sites (about 10-20%) and rarely the oral mucosa. Non-anogenital forms occur on the trunk, neck, shoulders and arms usually taking a guttate form (6).

This mucocutaneous disorder shows an overall prevalence of up to 1% to 4% of the population (8).

Aetiology and pathogenesis

Although the exact aetiology of the disease remains unknown, the autoimmune cause is the most reported. First of all, there is a clear association between lichen sclerosus and other autoimmune disorders, up to 34% of patients (7). Up to 74% of patients have been found to have autoantibodies (6). The most commonly associated diseases are alopecia areata, vitiligo, autoimmune thyroditis and pernicious anaemia (6). The prevalence itself, higher in women than in men, seems to confirm the autoimmune hypothesis.

Genetic factors have also been advocated to explain the aetiology of lichen sclerosus, specially after the evidence that familial cases have been reported, in fact the prevalence of the disease is very higher in monozygotic and non-identical twins, as firstly reported by Meyrick Thomas and Cox in '80s (9, 10).

Afterwards, when immunogenetic studies developed, a significant association with the HLA class II antigens has been discovered (11). The HLA complex is known to determine the susceptibility to the inflammatory diseases: lichen sclerosus is strictly associated with the haplotypes HLA-DQ7, HLA-DQ8 e HLA-DQ9 (11). These haplotypes are also responsible of the site of the body involved and the extension of the lesion, and, more interestingly, are likely to determine malignant transformation (12). The crescent interest in the genetic aetiology head to the study of cytokines. In this field, the polymorphism of the interleukin-1 receptor antagonist gene has been advocated: particularly, the gene itself and the number of the alleles are considered possible causes of the severity of the disease (13).

The spirochaete *Borrelia* has been implicated in the intent to explain lichen sclerosus aetiology particularly *Borrelia afzelii*. The *Borrelia* itself and anti-*Borrelia* antibodies have been isolated in the skin lesions, in different percentage according to the geographic provenience of the patients. The response to the antibiotic therapy, based on penicillin, is the main topic in favour of the possible relationship between *Borrelia afzelii* and lichen sclerosus. Moreover, the aspect of the lesions, similar to the lesion provided by Lyme disease (whose aetiologic agent is *Borrelia burgdorferi*), might suggest that *Borrelia* is involved in lichen sclerosus.

Nevertheless, studies with PCR leaded to conflicting results, so that this hypothesis is not generally accepted. Viral agents have also been thought to be possible causes of lichen sclerosus: Drut and coll. detected the presence of *Papillomavirus* in the skin lesions (14).

An important mechanism which plays a role in lichen sclerosus is the Koebner phenomenon, i. e. the history of a skin traumatism occurring 1-2 weeks before in the same site of the lesion (15). A lot of molecules are responsible of this skin reaction: some cytokines delivered from cheratinocytes, such as TNF-α and interleukine-6, and some cheratinocyte proteases. Then, the neuropeptides delivered from neuronal tissue, such as SP and VIP, may activate the endothelium, so leading to the expression of adhesive molecules (such as ICAM-1) and the consequent lymphocytes activation and local skin inflammation (16).

Koebner phenomenon is often due to repeated microtraumatism, such as the shoulder-strap of the brassiere in women.

Finally, the evidence that lichen sclerosus is more frequent in post-menopausal age suggested a hypothetic role of oestrogen in its pathogenesis, although there is no relationship between lichen sclerosus and pregnancy, hysterectomy, contaceptive therapy or HRT in women (17).

In 1984, Friedrich and Klara reported a defect of 5α-reductase in androgen metabolism of women with lichen sclerosus, but topic therapy with testosterone did not give place to any benefit (18, 12).

To date, hormones cannot be considered responsible of the disease.

Histological feature

Lichen sclerosus shows particular histological features, that make it possible to be distinguished from other skin and mucosal diseases, such as lichen planus, pemphigoid and morphea. Biopsy is also fundamental, as it makes the specialist sure to rule out malignancy.

Macroscopically, lichen sclerosus is characterized by pallor associated with textural changes such as atrophy or hyperkeratosis. Telangiectasia and purpura are common, also (6).

Generally, the lesions are grouped in plaques: in the elder ones, the skin is atrophic and seems compressed; bowel features or haemorrhagic aspect can appear. On the surface of the involved skin, it might be visible whitish keratosic material coming out from pilipher follicoles. Skin fissures might occur with sexual intercourses and defecation.

Histological features include hydropic degeneration of the basal cells and pale-staining homogenous zone in the upper dermis. Thinning of the epidermis with flattening of the rete-ridges, oedema and homogenization of the collagen in the upper dermis are usually found.

An important aspect of the histological pattern of lichen sclerosus is also the inflammatory infiltrate. Perhaps, it is initially present near the dermo-epidermical junction and then it moves downwards, so involving all zones of the skin (19, 20). The inflammatory infiltrate is made up of CD4+ and CD8+ lymphocytes in equal proportions, but macrophages and mast cells are also present. Mast cells, in particular, are responsible of the pruritus (21, 12).

Electron microscopy has not a usual role in the diagnosis, but it gives provides important information to understand the structural modification of the skin. In fact, it evidences structural changes in collagen fibrils, as a result of the loss of the cross striations and the presence of collagen immature forms. Moreover, there is a different distribution of the fibronectin, which is lower in the papillary dermis and increased in the deep dermis (22). Similarly, we have an increase in tenascin, a molecule also involved in wound repair and in skin cancer (12).

Lichen sclerosus and Squamous Cell Carcinoma (SCC)

An important association between lichen sclerosus and Squamous Cell Carcinoma (SCC) has been reported. The past history of the patients affected by lichen sclerosus revealed systemic cellular immunomediated disregulations, which may theoretically create a permissive environment for the development of squamous cell carcinoma (23).

The association between lichen sclerosus and SCC has been reported in about one half of cases and in some cases the diagnosis of lichen sclerosus preceded the diagnosis of SCC by about 10 years (24).

Conversely, lichen sclerosus in males is most reportedly associated with specific forms of SCC, such as pseudohyperplastic SCC and it preferentially originates in penile foreskin mucosa (25, 26).

Noteworthy, the association has been reported for anogenital lichen sclerosus only, because extragenital lichen sclerosus does not seem to carry a risk of malignant change (25).

It is generally accepted that there is a relationship between Human Papillomavirus (HPV) and SCC. HPV has been found in most cases of lichen sclerosus both in women and in men. Moreover, high-risk HPV 16 is the predominant HPV detected in lichen sclerosus (27).

HPV is known to contribute to tumoral transformation predominantly through the activation of the viral oncoproteins E6 and E7, which lead to the overexpression of protein p16, a cyclin-dependent kinase inhibitor (28).

HPV is often present in lichen sclerosus skin and mucosal lesions and near the margins of the lesions, but in anogenital lichen sclerosus only: there is no relationship between HPV and extragenital lichen.

As a marker of HPV activity, the protein $p16^{INK4A}$ has been particularly studied in penile cancer: reportedly, its expression is correlated with HPV detection and occurred in 29% of penile Squamous Cell Carcinoma (SCC) (27, 29).

Nevertheless, we can maintain that vulvar SCC linked to lichen sclerosus cannot be outspokenly associated with human papillomavirus. However, we are sure that high-risk HPV infection occurs in both

lichen sclerosus and squamous cell carcinoma and is associated with $p16^{INK4A}$ overexpression. This is the reason why the prophylaxis with HPV vaccines is fundamental.

Besides $p16^{INK4A}$, cycloosygenase-2 (COX-2) overexpression has been advocated to explain the evolution of vulvar lichen sclerosus to SCC.

The role of angiogenesis in tumoral progression is wall known. Angiogenesis may be assessed by microvessel density (MVD) and is sustained by Vascular Endothelial Growth Factor (VEGF), a 32-42 kDa, heparin-binding glycoprotein which plays a role in stimulating angiogenic activity *in vivo* and *in vitro* (30).

In the last decade, interest aroused in COX-2 expression and in its supposed relationship with angiogenesis.

Angiogenesis is poorly expressed in unchanged cases of lichen sclerosus, and these cases do not express neither VEGF nor COX-2.

Precursor lesions as VIN have often been found within an area of lichen sclerosus or around it. In these sites, VEGF and COX-2 activity are generally increased, this suggesting that they may contribute to lichen sclerosus evolution to SCC (31, 24).

Clinical features

Although a significant number of patients are asymptomatic (9%) (6) and the disease is observed at the routine examination, most frequently women refer intractable pruritus, irritation, dyspareunia, soreness and dysuria. Painful skin fissures can occur with sexual intercourses and defecation.

In men, instead, the most referred symptoms are tightening of the foreskin, sometimes resulting in phimosis, painful erections and decreased penile sensitivity, and urinary obstruction.

Specially for women, lichen sclerosus has detrimental effects on quality of life, although a lot of patients come to the specialist when the lesions are already in advanced stage and it is more difficult to treat them.

The observation of the lesion evidences the typical skin changes: areas of pallor, which may be small polygonal patches or large plaques, thinned, atrophic, wrinkled and fragile, with possible telangiectasia, purpura erosions, tender fissures in the labial sulci and perineal area, and rarely, haemorrhagic blisters (12). Hyperkeratosis and sclerosis are frequent, too.

The labia minora may fuse and the clitoris may become buried: nevertheless, vaginal and cervical tissue are not affected.

Noteworthy, it is possible that the signs of lichen sclerosus are similar to the signes of sexual abuse: this is the reason why it is very important to pay attention to clinical features in prepubertal girls (32). Sometimes, at menarche, symptoms and signs of lichen sclerosus improve spontaneously. However, no data are available neither about the long-term risk of relapses of lichen sclerosus at about the long-term risk of the evolution to SCC in these patients.

In men, the sites usually affected are glans penis and foreskin; involvement of the perianal region is rare. Frequently, men present with non-retractile penis and the appearance of balanitis. Sometimes, they present in need of circumcision (12).

Appropriate pharmacological management of lichen sclerosus

We think that the management of lichen sclerosus performed in our division is one of the most appropriate to give the patient relief from the disease and to follow-up its possible malignant change. First of all, we have to say that if the lesions are non complicated, our approach is pharmacologic; instead, if the patient complains important functional involvement, the treatment might be surgical.

Suspicion of lichen sclerosus may be founded on the clinical features only, but the correct diagnosis must be supported by the biopsy: this makes the specialist sure his/her diagnosis is correct and gives information about the presence of tumoral cells.

If the biopsy is negative for neoplastic degeneration, and the treatment may be pharmacological only, we recommend topic therapy with clobetasol propionate 0,05% once a nignt for 4 weeks, then alternate nights for other 4 weeks, and finally for 4 weeks twice a week. After three months, the patient is examined

again and if it has improved, clobetasol should be used only when required.

It is important that the patient quickly reports refer an improvement of the pruritus: this confirms that the treatment may be appropriate.

In total 30 gr. of clobetasol must be enough.

It is a good thing to add to the therapy an aqueous cream as a soap substitute. A good intestinal toilet is also important in order to improve defecation symptoms.

Other pharmacological treatments are possible: for example, beclomethasone diproprionate or diflucortolone valerate, but we recommend one of these just in case it is not possible to use clobetasol, only.

Surgical treatment of a particularly interesting case of vulvar lichen sclerosus

The normal appearance of the vulva varies depending on age and racial factors. Lichen sclerosus is an inflammatory disease of the skin with a predilection for the external genital and it most commonly affects women in post-menopausal age.

At physical examination, our patient, S. C., 68 years old, presented with labial fusion, burial of the clitoris and severe introital stenosis (Fig. 1).

The patient complained stiping and barling passing water, obstructive dysuria, and necessity of plerum abdominale. In the last few months, the urinary symptoms complicated in recurrent cystitis and stress incontinence.

The scalp, the oral cavity, the back and the inguinal region were involved in a process of lichen planus firstly diagnosed in 1992. In the same year, the patient underwent a perineoplasty because of the labia fusion. Then, the patient was pharmacologically treated with topic clobetasol only. Unfortunately, she has not undergone a periodic follow-up for 12 years: when we met the patient again some months ago, she presented a complete fusion of the labia maiora and the clitoris was not visible.

The past history of the patient involved the Basedow disease. Menopause at 48 years without HRT, PARA 2002.

Surgical technique: The patient lied in dorsal lithotomic position and surgery was performed under spinal anaesthesia. Antibiotic therapy (ceftriaxone) was infused early in the morning as prophylaxis. In the inguinal region a semilunar cicatrix was present, due to previous surgery: it passed over the anus and stopped at the pubes.

We performed to the dissection of the buried clitoris, the separation of the fused labia and the enlargement of the narrowed introitus (Fig. 2 and 3).

The longitudinal incision was gradually performed in the deep tissues and when the urethra was seen, it was immediately catheterized by Olivaire 10 Ch. Urethral canal was progressively dilated and calibrated until 18 Ch., then a Foley 18 Ch. was inserted.

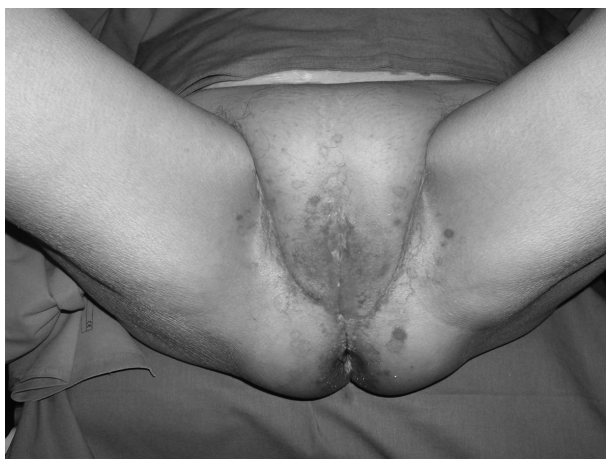

Figure 1. Vulvar lichen sclerous before surgery

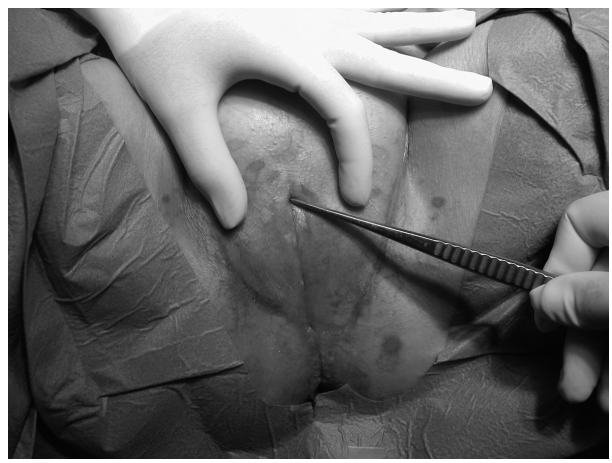

Figure 2. Fused labia before dissection

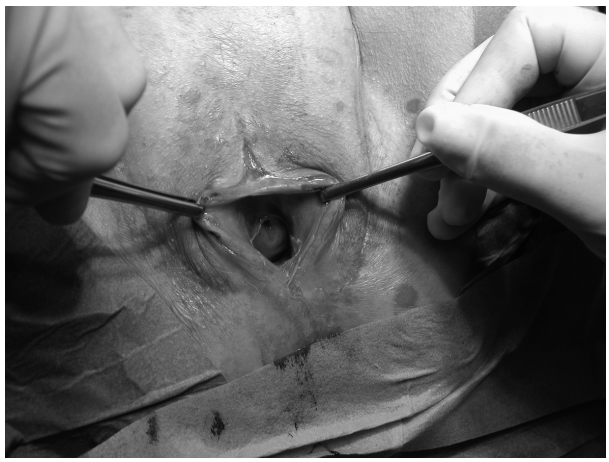

Figure 3. The dissection of the fused labia

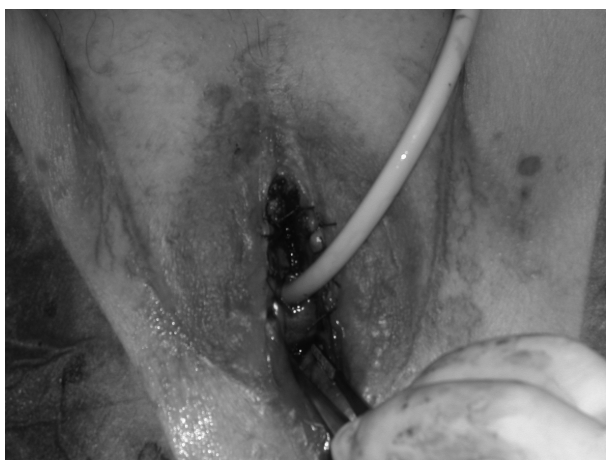

Figure 4. Vaginal introitus after surgery

Anterior perineum was then reshaped with good results (Fig. 4).

Conclusions

Lichen sclerosus is a chronic immuno-mediated skin disease of the genital region in men and women. An important relationship between lichen sclerosus and vulvar squamous cancer is reported in literature. The association between lichen sclerosus and SCC has been reported in 50% of cases.

If the biopsy is negative for neoplastic degeneration and the treatment may be pharmacological only, we recommend topic therapy with clobetasol propionate; alternatively, beclomethasone diproprionate and diflucortolone valerate may be used. In our work, we described the case of a patient, S. C., 68 years old, preventing with vulvar disease and labial fusion, burial of the clitoris and severe introital stenosis. In this case, the treatment was surgical. We performed the dissection of the buried clitoris, the separation on the fused labia and the enlargement of the narrowed introitus. The urethra was progressively dilated and anterior perineum was then reshaped with good results.

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