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Review Article

Modern Concepts of Lichen Sclerosus of the Vulva

SI Surkichin[1]*, LS Kruglova[1], IA Apolikhina[2], RYu Mayorov[1] and M Avin[3]

[1]*Central State Medical Academy of the Administrative Department of the President of the Russian Federation, Moscow, the Russian Federation*

[2]*National Medical Research Center for Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov, Moscow Russian Federation*

[3]*Medical Center "Stolitsa", Moscow, Russian Federation*

***Corresponding Author:** SI Surkichin, Central State Medical Academy of the Administrative Department of the President of the Russian Federation, Moscow, the Russian Federation

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Abstract

Lichen sclerosus is a chronic inflammatory disease of mucous membrane, characterized by hypopigmentation and skin atrophy. Morbidity in women has two peaks: the first - between 8 and 13 years, the second - in the fifth and sixth decades. Average age at diagnosis ranges from 52 up to 60 years old. The pathogenesis of lichen sclerosus is based on the infiltration of activated T cells that synthesize interleukin 4 (IL-4) and transforming growth factor β (TGF β). These cytokines activate fibroblasts, which produce altered collagen, leading to fibrosis. The diagnosis is based on a thorough history, which includes information about the presence of autoimmune diseases in the patient and his family, examination of the mucous membranes, extragenital skin, as well as gynecological examination. Thus, the diagnosis of lichen sclerosus is usually is clinical. For genital lichen sclerosus, the gold standard of treatment is a three-month use of topical glucocorticoids (strong or very strong). Symptoms improve, as a rule, by 75–95%. More often than others, clobetasol propionate 0.05% is used in the form of an ointment or cream 1-2 times a day for the first month, during the second month - every other day, within third month - 2 times / week. As a maintenance therapy, glucocorticoid ointment is used 1-2 times / month, and 0.1% mometasone furoate ointment may require application 2-3 times / week. Second-line therapy includes topical calcineurin inhibitors and imiquimod. Calcineurin inhibitors are prescribed for patients who do not tolerate topical glucocorticoids or do not respond to such treatment. Vulvar Cancer Risk Remains Increased throughout the woman's life, therefore the patient must see a doctor every 6-12 months, provided that symptoms have stabilized, there is no sexual impairment, and there is no further anatomical deformity.

Keywords: *Modern Concepts; Lichen Sclerosus*

Brief description, etiology

Lichen sclerosus was first described French dermatologist François Henri Gallopeau (François Henri Hallopeau) in 1881. Since then, terms such as leukoplakia, vulvar kraurosis, obliterating xerotic balanitis, lichen sclerosus, dystrophy. In 1976, the International Society for the Study of Vulvovaginal Diseases adopted the term lichen sclerosus.

Lichen sclerosus is a chronic inflammatory disease mucous membrane, characterized by hypopigmentation and skin atrophy. Most often, lichen sclerosus affect genital skin, less often - extragenital plots. Lichen sclerosus are 6-10 times more common in women than in

men [1]. The disease can cause phimosis or scarring of the vaginal opening. Diagnosis is clinical, but often a biopsy is required to confirm it. The lichen sclerosus leads to the destruction of anatomical structures, functional disorders and has a potential risk malignant transformation. Treatment and long-term follow-up are mandatory.

Lichen sclerosus belong to the class of autoimmune diseases, however, its etiology is still unknown. Given the association with other autoimmune diseases, such as alopecia, vitiligo, autoimmune thyroiditis and pernicious anemia, the etiology of lichen sclerosus is probably multifactorial. The most common association is with autoimmune thyroiditis [2]. It is believed to be played role genetic predisposition, infectious agents (spirochetes), sex hormones and the Kebner phenomenon [3]. Studies have examined the role of both infectious agents such as Borrelia burgdorferi, human papillomaviruses, hepatitis C, Epstein – Barr viruses, however, no confirmation has been received [4-6].

With lichen sclerosus, autoantibodies to protein 1 of the extracellular matrix [7] and to the basal membrane (BP180 and BP230) (30–80% of cases) [8, 9], as well as antithyroid antibodies [10].

Epidemiology

The exact prevalence of lichen sclerosus is unknown, although in the literature it is reported that in the general population the indicator ranges from 1/1000 to 1/300 people [10]. In specialized centers for the treatment of vulvovaginal diseases, the indicator ranges from 7-26% [11]. Lichen sclerosus meets in patients of both sexes, but more often in women in a ratio with men from 1: 1 to 10: 1. Morbidity in women has two peaks: the first - between 8 and 13 years, the second - in the fifth and sixth decades. Average age at diagnosis ranges from 52 up to 60 years old. The lichen sclerosus is localized more often on the skin of the genitals - in 85-98% of cases, in the extragenital area - only in 15-20%. [2] Extragenital localization are extremely rare in childhood. The literature contains single descriptions of mucosal lesions oral cavity, the so-called lichen sclerosus oral cavity.

Pathogenesis, clinical presentation

The pathogenesis of lichen sclerosus is based on the infiltration of activated T cells that synthesize interleukin 4 (IL-4) and transforming growth factor β (TGF β). These cytokines activate fibroblasts, which produce altered collagen, leading to fibrosis. In addition, a decrease in the number of capillaries, leading to vascular damage. Interleukin 1 (IL-1) and its receptor antagonist (IL-1ra) are also involved in the pathogenesis of lichen sclerosus, as well as an increase in the number of monoclonal T-lymphocytes CD4 +, T-dendritic lymphocytes CD1a + cells, macrophages, mast cells and a decrease in the number of T-lymphocytes CD3 + [12]. In the literature, there are also indications of an increase in the number of circulating autoantibodies of immunoglobulin G (IgG) against extracellular matrix protein 1 (ECM 1), which leads to the deposition of hyaline material in the dermis [13]. The lichen sclerosus has a specific histological picture, characterized by striated lymphocytic infiltration below the zone of skin edema and orthokeratotic hyperkeratosis. Histopathology results vary depending on the duration of the disease.

In the earlier stages of the lichen sclerosus, it manifests itself as a vacuolar degeneration of the basal layer, hyalinization of subepithelial collagen, decrease in elastic fibers in the upper dermis, and dilation of blood vessels under the basement membrane. With more old lesions, histology shows a reduced number of mononuclear cells and scattered islets of mononuclear cells in hyalinized dermis [12,13].

The lichen sclerosus most often affects the genital area, less often - extragenital. Typical lesions begin with sharply defined erythema, which then becomes hypopigmented, ivory white, “porcelain”, with the appearance of sclerotic plaques. Plaque may subsequently thicken due to repeated excoriation. Itching is basic symptomatic and often worse at night. Other symptoms include telangiectasias, purpura, fissures, ulcers and swelling. Typical complaints include significant itching, local burning, pain, painful bowel movements. Constipation is more common in children. However, the disease can be asymptomatic.

The lesion begins around the periclitoral hood and varies from local to extensive, covering the entire area of the vulva, perineum and perianal part, giving it the characteristic appearance of a "sign keyhole ". The vagina and cervix remain intact. In girls, lichen clerosus use usually manifests itself as irritation and soreness that mimics sexual abuse. Extragenital lesions occur on any part of the skin and are usually asymptomatic, most often the areola are involved zone, neck, wrists, hips, upper back and shoulders. Clinical lesion of the oral mucosa manifests itself as bluish-white papules on the mucous membrane the shell of the cheek or under the tongue [1].

Diagnostics

The diagnosis is based on a thorough history, which includes information about the presence of autoimmune diseases in the patient and his family, examination of the mucous membranes, extragenital skin, as well as gynecological examination. Thus, the diagnosis of lichen sclerosus is usually is clinical. In some cases, it may biopsy done, but atypical histology does not exclude a diagnosis.

A biopsy should be performed if atypical clinical picture, with suspicion of malignancy and lack of response to the recommended first-line treatment of appropriate duration. Diagnosis of other autoimmune diseases is required in accordance with the symptoms identified in the study of thyroid function.

Foreskin adhesion can lead to phimosis and the subsequent disappearance of the clitoris and, as a consequence, the formation of smegmatic pseudocysts. Pseudocysts resulting from delayed smegma between the clitoris and the foreskin may enlarge, become painful, and become infected. In cases where over the urethra occur synechia or fusion of the labia minora, then urinary flow is impaired and / or recurrent urinary tract infections develop [14].

In addition, in 5% of cases, lichen sclerosus can be transformed into squamous cell carcinoma of the vulva [15]. Study P. Halonen., *et al.* [15] showed that the most pronounced risk of malignancy was recorded in the first year observation, although most cancers occurs after 5 years of observation. At the same time, women at the age of 30 had the highest risk of lichen sclerosus transformation into cancer, even though the disease develops more often in older women. The authors believe that the increased risk in the first year can be attributed to the fact that young women seek help for symptoms associated with vulvar cancer, but not with lichen sclerosus. The same study was the first to report a high risk of developing vaginal cancer and a low the risk of oral cavity and skin cancer [15].

The precancerous lesion associated with lichen sclerosus is a differentiated type of intraepithelial neoplasia of the vulva. This type of disease is cause of most types of vulvar cancer, although it is much less common (2 - 10% of cases) than squamous cell high grade intraepithelial neoplasia of the vulva (HSIL). The incidence of differentiated vulvar intraepithelial neoplasia may be underestimated due to LS underdiagnosis or due to rapidly progressing invasion [16,17]: the ten-year risk of progression is estimated at 18% [18]. Some studies suggest a weak association of lichen sclerosus with vulvar melanoma (including in children), basal cell and verrucous carcinoma [19].

Treatment

Currently, there is no single strategy that could be recommended for the treatment of lichen sclerosus [20].

Treatment	Effect	Degree evidences
Glucocorticoids	Clobetasol propionate (3 months) — 75% improvement Full resolution of symptoms — 20%	1+/A
Glucocorticoid Injections	80% improvement after 4 injections	1+/B
Estrogen	Ineffective	–
Progesterone, 2% (8%)	10% (up to 60%) improvement	1+/A
Cyclosporine	20% improvement	3/D

Tacrolimus, 0.1%, 0.03%	34% response after 12 weeks, 29% partial response after 24 weeks.	1+/B–A
Pimecrolimus, 1%	70% complete response, 25% partial relief of symptoms after 3 months	1+/B
Retinoids	50-60% full response, 20-30% partial	3/D
Calcipotriol	No data available	–
Oxatomide	Itching relief	3/D
Moisturizing products	10% improvement	2+/3/D
DermaSilk (United Kingdom)	Fewer symptoms compared to cotton products	2+/C
UVA1	There are reports of efficiency	–
Photodynamic therapy	There are reports of efficiency	3/D
Glucocorticoids	No data available	–
Retinoids	35-85% efficiency	1+/B
Cyclosporine	Effective	3/D
Methotrexate	Effective	3/D
Hydroxyurea	Effective	3/D
Fumarate	No data available	–
Antibiotics	There are reports of efficiency	–
Vitamin A/E	Less effective than moisturizers	–
Vitamin B10	No better than a placebo	–
Surgery		
Surgical excision	Possible complications	–
Perineotomy	With vaginal stenosis, improvement of quality of life in 80-90% of cases, no long-term results	3/D
With laser	With symptomatic clitoral phimosis	3 D
Stem cells	Further study is needed	–

Table 1: *Effectiveness of various methods of treating lichen sclerosus.*

The goal of treatment is to relieve symptoms, stop atrophy, prevention of scarring and anatomical distortions, as well as malignant transformation. Therapy includes general care, topical and systemic medications, and surgical procedures. It is important to inform the patient to avoid the use of irritating detergents such as like soap, and preferred emollient products, including including emollients to break the itch – irritation cycle [21]. In about 1/5 of cases, complete remission of the disease is observed. Girls usually get better with the onset of puberty, although scarring may not dissolve. In a significant number of cases later relapses occur [22]. Treatment inhibits the progression of atrophy and scarring. There are reports that women adhering to prescribed treatments, less are prone to developing vulvar cancer. These data confirm the need for treatment of lichen sclerosus of the vulva even in asymptomatic women, especially if they have progressive atrophy, cracks, hyperkeratosis and ecchymosis [23].

For genital lichen sclerosus, the gold standard of treatment is a three-month use of topical glucocorticoids (strong or very strong). Symptoms improve, as a rule, by 75–95%. More often than others, clobetasol propionate 0.05% is used in the form of an ointment or cream 1-2 times a day for the first month, during the second month - every other day, within third month - 2 times / week. [24]. Super

strong steroids cannot be used in daily regimens more than 3-4 weeks. not only due to the risk of complications, but also the risk of developing tachyphylaxis. There appears to be no benefit to using glucocorticoids more than once daily. Ointment bases preferable to cream, since the latter are more often lead to sensitization and irritation [25].

As a maintenance therapy, glucocorticoid ointment is used 1 - 2 times / month, and 0.1% mometasone furoate ointment may require application 2 - 3 times / week. [20]. Women should be advised that the maximum acceptable dosage for this topical glucocorticosteroid is 60 - 120 g / year. Considering that every application (half of the "fingertip") is equivalent to 0.25 g, the maximum number of days per year for using the LS is about 240, or 2/3 [20].

Second-line therapy includes topical calcineurin inhibitors and imiquimod. Calcineurin inhibitors are prescribed for patients who do not tolerate topical glucocorticoids or do not respond to such treatment. Despite the proven safety of their daily use during 6 months, there are concerns about the possible increased risk of malignant neoplasms. It may take up to 12 weeks to achieve remission of lichen sclerosus. Calcineurin inhibitors have been shown to effectively control the signs and symptoms of lichen sclerosus, however corticosteroids appear to allow achieve an effect with a greater likelihood of complete remission [26]. Systemic methods of treatment are used for severe, forms of lichen sclerosus that do not respond to local treatment. Glucocorticoids have been shown to be effective in only one research when used in conjunction with methotrexate. Other treatment options include retinoids (acitretin, isotretinoin, or etretinate), methotrexate, and cyclosporine. Before you start taking one of these lichen sclerosus, the diagnosis must be confirmed biopsy, and treatment should be initiated by a physician specializing in vulvar disease [20]. In women with vulvar lichen sclerosus and local pain that persists despite treatment with glucocorticoids, oral tricyclic antidepressants (amitriptyline, desipramine, nortriptyline) help reduce discomfort at a dose of 10 mg, which is lower than with treatment depression, however, for a lasting effect, the duration treatment is up to several weeks. Surgical intervention is used exclusively for the treatment of complications, since the disease tends to relapse after excision or even tissue transplantation (40 - 50% cases) [27].

Indications for vulva surgery in women with lichen sclerosus usually fit into one of 4 categories: treatment precancerous or malignant lesions; dysfunction of the urinary tract; sexual dysfunction; acute infection. With extragenital lichen sclerosus, therapeutic options are limited and include phototherapy, topical steroids, 0.1% tacrolimus ointment, and systemic steroids or methotrexate. Patient monitoring required (table) [28]. Since lichen sclerosus cannot be completely cured, disease progression must be monitored. It is believed that it is possible to achieve complete resolution of ecchymosis and thickening of the skin, however with its paleness. it is impossible to cope today [24].

The first visit from the start of lichen sclerosus treatment should be no later than 3 months, and the next - no later than 6 months.

Conclusion

Vulvar Cancer Risk Remains Increased throughout the woman's life, therefore the patient must see a doctor every 6-12 months, provided that symptoms have stabilized, there is no sexual impairment, and there is no further anatomical deformity. Otherwise, you must immediately see a doctor. Visits should be more frequent if intraepithelial neoplasia is diagnosed vulva. Ideally for monitoring the development of the disease the filing cabinet must contain photographs taken in dynamics.

Additionally

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