Polish Annals of Medicine

Journal homepage: https://www.paom.pl

Review paper

Lichen sclerosus: A review of the literature

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Article info

Article history
Received 3 January 2020
Accepted 18 September 2020
Available online 4 November 2020

Keywords
Lichen sclerosus
Balanitis xerotica obliterans
Kaurosis vulvae

Doi
https://doi.org/10.29089/2020.20.00131

Abstract

Introduction: Lichen sclerosus (LS) is a chronic inflammatory dermatosis which may lead to scarring and atrophy of the tissues. It has predilection for the skin and mucoses of anogenital area in men, women and children. The extragenital lesions occur less frequently. The most common symptoms are itching, pain and dyspareunia. The true prevalence of this disease is unknown and probably underestimated due to the underdiagnosis. Therapy of LS often causes many difficulties.

Aim: The aim of our review of the literature is to discuss the diagnostic and therapeutic difficulties of LS that may come across doctors of various specializations. We reviewed the literature regarding the etiology, clinical, medical and surgical management of LS.

Material and methods: We performed a comprehensive research of the literature in PubMed, Medline and other electronic databases between 1956–2019 using the key words: 'lichen sclerosus,' 'balanitis xerotica obliterans,' 'kaurosis vulvae.' We reviewed 54 articles.

Results and discussion: The clinical features and the management vary depending on the age and sex of the patient. To properly treat and prevent possible complications of LS, an interdisciplinary approach to patients care and timely diagnosis of the disease are extremely important. The essence of treatment is to control symptoms, prevent and treat complications and search for early signs of cancer.

Conclusions: LS is a disease that presents numerous challenges for doctors specializing in dermatology, gynecology, urology and pediatrics. An interdisciplinary approach is crucial to achieve therapeutic success and patient's satisfaction.

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1. INTRODUCTION

Lichen sclerosus (LS) is a chronic inflammatory dermatosis which may lead to scarring and atrophy of the tissues. It has predilection for the skin and mucoses of anogenital area in men, women and children (83%–98%). The extragenital lesions occur less frequently (15%–20%).[1,2] The initial whitish patches and nodules usually develop into large, white patches of atrophic skin. The most common symptoms are itching, pain and dyspareunia. LS was first described by Hallopeau in 1887. The true prevalence of this disease is unknown and probably underestimated due to the underdiagnosis (one third of the cases can be asymptomatic) and patients are distributed among different specialists (gynecology, dermatology, urology, pediatrics). The estimated prevalence in adult women is up to 3%, in men 0.07%. LS may occur at any age.[3] Woman mostly show two morbidity peaks: prepubertal and postmenopausal. In male patients it appears in both young boys and adult men.

2. AIM

The aim of our review of the literature is to discuss the diagnostic and therapeutic difficulties of LS that may come across doctors of various specializations. We reviewed the literature regarding the etiology, clinical, medical and surgical management of LS.

3. MATERIAL AND METHODS

We performed a comprehensive research of the literature in PubMed, Medline and other electronic databases between 1956 and 2019 using the keywords: 'lichen sclerosus,' 'balanitis xerotica obliterans,' 'kaurosis vulvae.' We reviewed 54 articles.

4. RESULTS AND DISCUSSION

4.1. Etiology

The etiology of LS is unknown, but it seems that the disease can be associated with genetic, infectious, hormonal and environmental factors. Familiar cases of LS have been reported, and immunogenetic studies revealed a significant association with the HLA DQ7 antigen. Of patients with vulvar LS, 8%–39% report a family history of the condition and only 1% of male genital LS patients have a family history.[4] An increased incidence of tissue-specific antibodies (up to 74%)[5] and other comorbid autoimmune diseases, especially thyroid disease, have been observed in women suffering from LS.[6] Correlation has not been reported in men. A transcriptosome from LS of male anogenital area has excluded the expression of genes associated with autoimmune and infectious diseases.[7] In contrast, circulating anti-extracellular matrix protein (ECM-1) antibodies were found in both sexes.[8] The role for tumor necrosis factor α (TNF-α) in the pathogenesis of LS has been reported. There are some cases suggesting encouraging outcomes of the treatment of LS in male with adalimumab.[9] In men the coexistence of LS with high body mass index (BMI), coronary disease, diabetes and smoking was described.[10] LS has also been shown to be associated with injuries and chronic inflammation (the isomorphic phenomenon).[1] The skin lesions may occur at the points of pressure and friction exerted by underwear,[11,12] cycling,[13] rubbing or scratching, or due to repeated masturbation.[14] LS can also appear in old surgical and radiotherapeutic scars. The occurrence of skin lesions may be also caused by infections, including pinworms.[15,16] The role of *Borrelia* infection as an etiological agent remains controversial. Currently, there is no significant evidence for a connection between LS and *Borrelia burgdorferi*.[17]

4.2. Clinical manifestation

The diagnosis of LS is based on the typical clinical and histopathological features. The lesions characteristic for LS are hypopigmented porcelain-white well demarcated from the surrounding papules that coalesce into sclerotic plaques, often associated with extensive petechia areas, less often blisters. Hyperkeratosis is predominant. In the anogenital form of LS, the main complaints reported by the patients are itching and burning, which may increase in the evening and cause difficulties in falling asleep. There may also be pain and dyspareunia as a consequence of erosions and ruptures. The extragenital form is usually asymptomatic. Skin

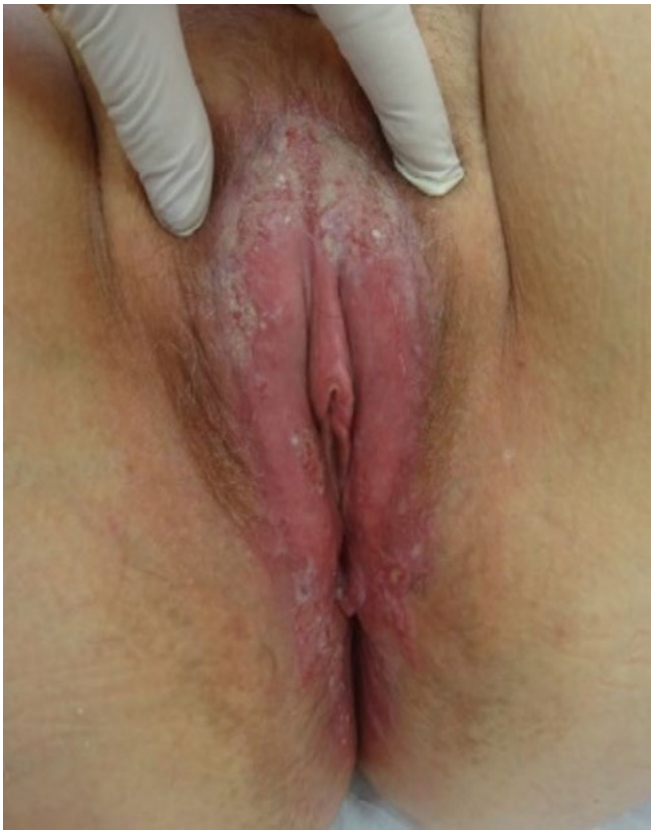

Figure 1. LS of the anogenital area in 34-year-old woman (lesions located on labia major, labia minor and vaginal vestibule). Involvement of the perianal area – 'eight symptom.'

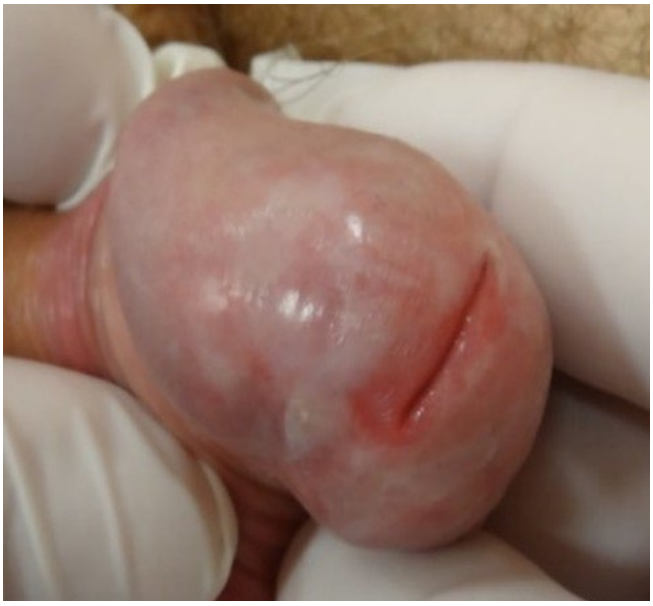

Figure 2. LS localized on the glans penis: white, multi--shaped, flat plaques.

lesions may occur anywhere on the body, although typical locations in extragenital form are the lateral surfaces of the neck, torso, armpits and arms. LS is a relapsing-remitting disease and has a slight correlation between clinical symptoms and the duration and severity of the disease.[18] The clinical features and the management vary depending on the age and sex of the patient.[19]

In adult women, lesions may be confined to the labia major, but usually involve and sometimes obliterate the labia minor and vaginal introitus. The anal area is affected in 30% of the patients, giving a characteristic figure of 'eight' or hourglass (Figure 1). The vagina and cervix are usually not involved, unless significant prolapse of the reproductive organs is observed.[20] In the course of the disease petechiae, blisters filled with bloody content, erosions and ruptures may form. In some cases, as a result of scarring, there may be complete atrophy of the labia minor and clitoris, restriction of vaginal entry and narrowing of the urethral opening (thus causing dysuria).[21]

For LS in prepubertal girls, the clinical features are similar to that found in adult women. The most common reported complaints are vulvar pain and pruritus. The perianal area is affected more often, which can lead to constipation and painful ruptures in the anal area. The lesions usually heal during puberty. No cases of carcinogenesis have been reported in affected areas, but scarring is possible.[22] The lesions may be similar to those seen in sexually abused patients. It is very important to always remember that these diagnoses are not mutually exclusive and appropriate measures should be initiated if sexual abuse is suspected, especially that sexual abuse may be the cause of LS (the isomorphic phenomenon).[23]

Genital LS in male is the most common in uncircumcised middle-aged men. The disease is usually confined to the glans penis and the prepuce or foreskin remnants. The penile shaft involvement is much less common and scrotal involvement is very rare. The first manifestation of the disease may be a sclerotic ring at the prepuce edge. The perianal area isn't typically occupied (Figure 2). Phimosis, painful erections and dyspareunia may occur due to lesions. In a prospective study of 75 patients with severe phimosis treated by total circumcision, eight (10.6%) have had histopathologically confirmed LS.[24] If the external opening of the urethra is involved, its narrowing and obstruction may occur. There have been reports of renal insufficiency due to obstruction of the external urethral opening, as a consequence of untreated LS.[25]

In boys, the penis is involved in 56% and the external urethral opening in 37% of patients with LS. The occupation of the perianal area, as in adult men, is extremely rare. Phimosis is the most common comorbid symptom. In a prospective study of 45 boys with acquired phimosis, up to 60% had LS, while in the study of 55 boys with congenital phimosis, LS was found in 30%.[26]

Typically, extragenital lesions are located around the neck, upper torso, armpits and arms. Rare locations include lips, face, scalp, hand, feet and nails.[1,27] The typical changes are porcelain-white papules, merging into larger, slightly hardened lesions, with variously pronounced follicular hyperkeratosis. The epidermis may separate from the dermis and form a blister (Figure 3).[19]

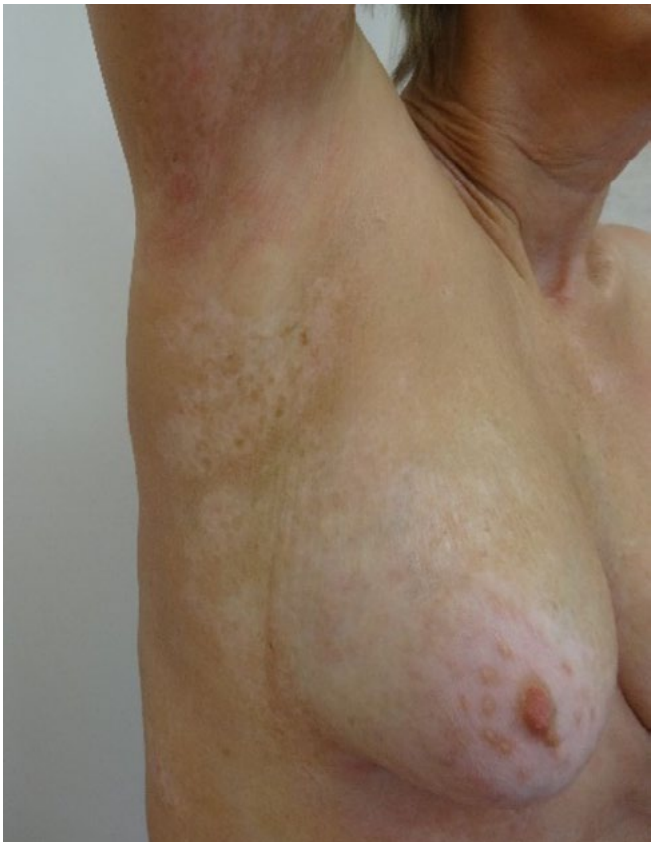

Figure 3. LS: Extragenital form; hypopigmented porcelain-white coalescing sclerotic plaques, well demarcated from the surrounding papules.

4.3. Risk of cancerization

In the genital form of LS, an increased risk of squamous cell carcinoma (SCC) is observed. For women, the risk ranges from 3.5 to 5%.[28] However, histopathological examinations of vulvar SCC indicate that about 60% of SCC develops from LS.[29,30] The lesions appear about 10 years after the first signs of LS and the age over 70 years is an important risk factor. In case of men, the incidence is also around 5%. The histopathological confirmation of LS can be found in 23%–40% of patients with diagnosed SCC of the penis. No cancerization was found in children with LS.[31,32]

4.4. Diagnosis

Diagnosis of LS is most often based on the clinical presentation and in cases with a typical course of the disease the biopsy is not necessary. The histopathological examination is recommended if atypical features occur, the disease doesn't respond to properly conducted treatment or there is a suspicion of cancer (persistent hyperkeratosis, erosions, erythema, new nodular or papular lesions). In young adult women, LS is less common, therefore, histopathological examination should be considered to confirm the diagnosis. The differential diagnosis of LS should include: acrodermatitis chronica atrophicans, anetoderma, atrophie blanche, atrophoderma of Pasini and Pierini, Bowen disease, child sexual abuse, complications of dermatologic laser surgery, cutaneous squamous cell carcinoma, cutaneous T-cell lymphoma, dermatologic manifestations of GVHD, erythroplasia of Queyrat, extramammary Paget disease, genital ulcerative disease, lichen nitidus, lichen planus, morphea, tinea versicolor, vitiligo. It is extremely important to remember that the biopsy material should be taken from the most active area of sclerosis.[19]

The histological picture of LS is characteristic and any differences result from the duration of the disease, the age of the patient and the location of the lesion. It is characterized by the occurrence of hyperkeratosis, significant thinning with loss of the normal rete ridge pattern, follicular plugging and atrophy of the epidermis. Vacuolar degeneration of the basal layer, loss of elastic fibers and vascular ectasia can be seen. The dominant feature is edema and homogenization of collagen just under the epidermis. These changes may extend to the middle layers of the dermis. Below there are streaked lymphocytic and histiocytic infiltrates. In contrast to anogenital one, the extragenital LS form is not associated with an increased risk of cancer transformation into squamous cell carcinoma.[33] Some authors consider that LS is a superficial variant of morphea occurring mostly in the genital area.[34] Although there are some similarities between LS and morphea, their exact relationship remains debated and those diseases are considered as separate entities.[35] Interestingly, there are studies which show that genital LS is significantly more frequent in patients with morphea than in controls.[35,36] The study performed by Kreuter et al. revealed that 5.7% of morphea (27 out of 472 cases) coexist with LS et atrophicus (LSA).[36] This result show that it is mandatory to perform a complete examination, especially of the genital mucosa in patients with morphea.

4.5. Treatment

To properly treat and prevent possible complications of LS, an interdisciplinary approach to patients care and timely diagnosis of the disease are extremely important. The essence of treatment is to control symptoms, prevent and treat complications and search for early signs of cancer. The treatment regimen of the anogenital form of LS should include:

(1) Minimizing irritants – replacing soap with other mild cleaning agents, avoiding artificial fabrics. Silk underwear rather than cotton one is recommended.
(2) Moisturizing with emollients or sodium hyaluronate.
(3) Treatment of co-existing infections.
(4) Use of corticosteroid anti-inflammatory therapy.
(5) In cases resistant to corticosteroids, topical calcineurin inhibitors, retinoids for hyperkeratotic lesions, or photodynamic treatment should be considered. In male – circumcision.
(6) In case of cancer – complete excision of the lesion.
(7) Providing psychological or psychiatric care to the patient.
(8) Long term observation.[18]

4.5.1. First line treatment

According to the guidelines of the British Association of Dermatologists regarding the management of LS, the gold standard in the treatment are superpotent and potent topical corticosteroids. It is recommended to use 0.05% clobetasole propionate in cream twice a day for 12 weeks.[19] The therapy reduces pain, itching and inflammatory infiltration. After the treatment, the reduction of epidermal atrophy and hyperkeratosis is observed. The erosions heal, the whitish plaques and roughness disappear. In addition, sensitivity to less potent corticosteroids increases. This therapy is safe and effective for both women and men.[4] Skin thinning and erythema may occur, but these changes disappear quickly after discontinuation of the treatment. Corticosteroids are also effective in children. It is reported that 70%–80% of boys with phimosis can avoid circumcision thanks to corticosteroid therapy.[37] Topical corticosteroid treatment can be safely used in pregnant and lactating women. In the case of slight scarring, natural delivery (with early episiotomy) is possible.[19] However, it is important to remember about possible side effects of chronic corticosteroid therapy such as: atrophy, formation of stretch marks, rebound reactions, fungal infections, reactivation of human papillomavirus (HPV) and herpes simplex virus infection or systemic absorption of corticosteroids. When the therapy is effective, local corticosteroids should be used as needed when symptoms of the disease recur. If symptoms persist after 12 weeks of treatment, it is recommended to check compliance, reconsider diagnosis (biopsy if needed) and continue topical therapy to control symptoms and prevent further scarring. The use of the second- and third-line treatment methods should be also considered (Table 1).

4.5.2. Second- and third-line treatment

There are few reports about positive effect on pruritus, disease progression and scarring by intralesional triam-

Table 1. Summary of LS treatment methods in adults.[4]

Treatment	Efficacy	
	Women	Men
First line treatment		
Topical corticosteroids (Clobetasol propionate)	Improvement in 75% after 3 months of treatment Complete remission in 20%	Improvement in 76% after 7 weeks of treatment Complete remission in 50%
Second line treatment		
Tacrolimus 0.1% or 0.03%	Complete response in 34% after 12 weeks Partial improvement in 29%	Complete response in 36% Partial improvement in 29%
Surgical treatment	Only when there are complications	90%–100% cure after circumcision
Third line treatment		
Retinoids	Complete response in 50%–60% Partial response in 20%–30%	No reports
Photodynamic therapy	Some effects are reported	Some effects are reported
Carbon dioxide laser	Some effects are reported	Some effects are reported
UV1 light	Some effects are reported	No reports
Platelet-rich plasma therapy	Some effects are reported	No reports
HIFU	Some effects are reported	No reports

cinolone acetonide injections.[38] It is also possible to use calcineurin inhibitors (tacrolimus, pimecrolimus), topical or oral retinoids (tretinoin, isotretinoin), antifungal drugs (cyclopiroxolamine), moisturizing agents with sodium hyaluronate (cicatridine), but the treatment with local potent corticosteroids remains the method of choice.[4]

There are studies which show reduction in symptoms by the use of a moisturizers. Regular use of emollients seems to be extremely important in local treatment. After the induction of remission with topical corticosteroids in women with vulvar LS, Cattaneo et al. observed good disease control through maintenance therapy with only emollient during the 24-week observation period. Emollients give symptoms relief after the initial treatment with topical corticosteroids.[39] As literature data suggests, topical testosterone, estrogen progesterone and hormone replacement therapy should not be used.[40]

Surgical procedures in women with anogenital LS should be limited to patients with vulvar intraepithelial and malignant tumors or to correcting scarring that impairs normal functioning. For LS in men who have failed first-line treatment, or if the disease has progressed resulting in structural changes due to scars, circumcision is indicated with the efficacy rate 76%–100%.[41] Some of the authors claim that total circumcision is the therapy of choice because it completely removes all the affected tissues and allows the regression of lesions.[42] The removal of the foreskin changes the local environment, which plays an important role in the etiopathogenesis of LS. The other surgical options are dilating or surgically correcting meatal stenosis and various urethroplasty techniques. An interesting research describes the group of 107 patients who underwent surgery for a LS urethral stricture, with excision of the involved urethra and replacement with grafts. In 42 (39%) of these cases skin (genital or not) was used for substitution and there was an almost 90% stricture recurrence rate during a long term follow-up. The other 65 patients (61%) underwent reconstruction with buccal and/or bladder mucosa and there have been no recurrences reported in longterm follow-up.[43] There are reports of using carbon dioxide laser as an alternative to an incisional surgery to ablate LS on the glans and for the dilatation of proximal strictures.[44,45]

Photodynamic therapy is a method that brings promising results in the treatment of LS. The term 'photodynamic therapy' (PDT) was used for the first time in the early XX century by von Tappeiner. It uses light of a specific wavelength, which activates the photosensitizer, causing the production of reactive oxygen forms that exert a cytotoxic effect on affected cells by necrosis or apoptosis. The advantage is the selective effect on the diseased cells. Three conditions must be fulfilled for the occurrence of photooxidation: the use of a photosensitizer which accumulates selectively in abnormal tissues, the presence of oxygen and the use of a light source emitting waves of the length absorbed by the used agent.[46] Among the photosensitizers available on the global pharmaceutical market, the majority are derivatives of porphyrins, chlorite and phthalocyanines. The first-generation photosensitizers include hematoporphyrin derivatives (HpD, Photofrin). The second generation is: 5-aminolevulinic acid (ALA) and its esters, benzoporphyrin derivative (BPD), lutetium texaphyrin, temoporfin (mTHPC, Foscan), tin ethiopururine (SnET2) and taloporfin sodium. The third generation includes compounds that are combinations of photosensitizers with monoclonal antibodies. The best-known topical photosensitizer is ALA. In most clinical PDT applications with current sensitizers, the required dose of light and irradiance are acceptable to the patient 37–200 J/cm^2, and the irradiation density doses 50–150 mW/cm^2 for wavelengths 630 nm, 650 nm and 670 nm. In clinical conditions, the exposure time is also limited to 15–20 minutes (Table 2).[47]

Table 2. The wavelength of light used in PDT.

Wavelength of light	Use in treatment
390–410 nm	Photodiagnosis and therapy of superficial lesions (eg acne)
625–640 nm	Therapy (first generation sensitizers: HpD, Photofrin, PPIX)
650–670 nm	Therapy (second generation sensitizers: chlorins, phthalocyanines)

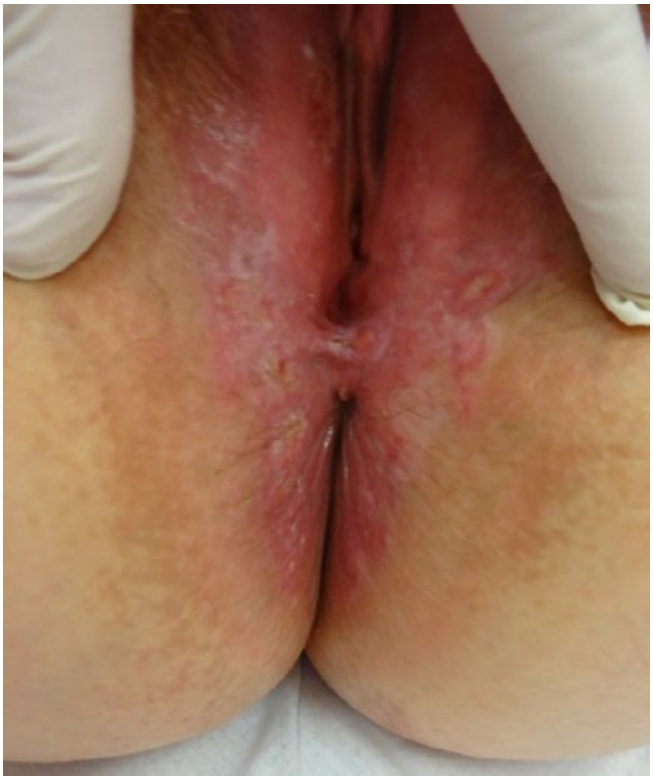

Figure 4. LS of the anogenital area: pre-photodynamic therapy; presence of erythema, edema, numerous erosions. The lesions were accompanied by severe itching and pain.

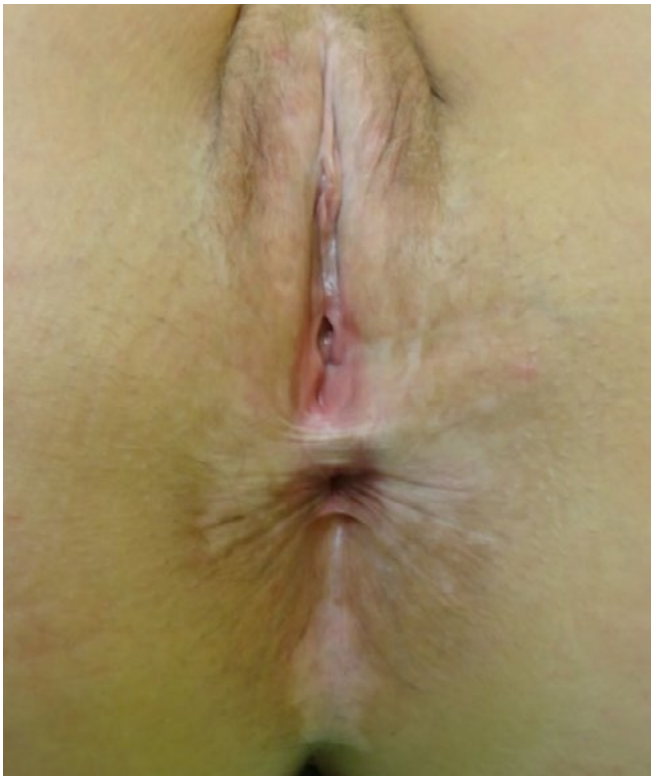

Figure 5. Condition after a cycle of three photodynamic therapy treatments. Visible reduction of inflammation, healing of erosions. Subjective complaints have completely disappeared.

Many descriptions of the effectiveness of photodynamic therapy are available in the literature.[48–50] The effectiveness of the abovementioned method is also confirmed by the authors' own experience (Figures 4 and 5). To date, there are no official recommendations for phototherapy of anogenital LS. The authors perform the procedure with the use of an LED lamp (red light with a wavelength of 635 nm), a dose of 40 J/cm^2 with a radiation intensity of 70%–80%, after applying an ointment with a photosensitizer (5-ALA) for 3 h. Depending on the effects of therapy, it is recommended to perform 1–5 treatments at intervals of several weeks.

There are also the first reports of the use of platelet-rich plasma therapy in the treatment of LS. The group of 31 patients suffering from LS participated in the study consisting of an injection of platelet-rich plasma. After 12 months of follow-up, an improvement was observed in 19 patients (62%), stable state in 11 patients (35%), and worsening of the disease in 1 patient (3%).[51] The use of UVA1 phototherapy in the treatment of LS is also studied. In 7 patients with severe vulvar LS, not responding to treatment with the strongest corticosteroids, UVA1 therapy was applied (340–400 nm at a distance of 30 cm, 65–74 mW/cm^2), irradiations were performed 3–5 times a week (15–65 exposures). A very good therapy effect was observed in two patients.[52] There are few reports about successful treatment of LS with CO_2 laser. Windahl have treated 62 patients with penile LS with carbon dioxide laser (15–20 W, defocused beam). During follow-up after an average of 30 months, 76% patients had no signs of disease.[53] Some authors report satisfactory results after treatment with focused ultrasound. Ruan et al. have treated 41 women with vulvar LS with HIFU (power range 3.0–4.7 W and frequency 9–10 MHz). After the treatment 13 patients were asymptomatic, 21 had improvement, in 7 there was persistent disease, 4 had recurrence.[54] Despite promising results, all those methods require further research.

5. CONCLUSIONS

(1) LS has a significant impact on patients' quality of life, especially sexual functioning.
(2) Patients should be informed on which changes (eg. ulceration) might indicate malignant transformation and mandate an immediate reevaluation.
(3) LS is a disease that presents numerous challenges for doctors specializing in dermatology, gynecology, urology and pediatrics. An interdisciplinary approach is crucial to achieve therapeutic success and patient's satisfaction.

Conflict of interest
None declared.

Funding
None declared.

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