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Treatment of genital lichen sclerosus in women – review

Leczenie liszaja twardzinowego w obrębie narządów płciowych u kobiet – przegląd

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Abstract

Lichen sclerosus is a chronic inflammatory skin disorder that belongs to a group of autoimmune connective tissue diseases, localized within the skin and mucous membrane of the anogenital area. In the latter location, the focal atrophy of the mucosa is the most visible sign. Lesions may be accompanied by symptoms such as itching, pain, burning. The disease occurs more often in females. The etiology is not fully understood. Genetic, infectious, hormonal factors and autoimmune mechanisms are taken into consideration. Early diagnosis and appropriate treatment is important to avoid further complications. This review aims to analyze available literature on the treatment of this disease entity.

Key words: **lichen sclerosus** / **genital organs** / **treatment** /

Streszczenie

Liszaj twardzinowy jest przewlekłą chorobą zapalną należącą do grupy autoimmunologicznych chorób tkanki łącznej, lokalizującą się w obrębie skóry, oraz błon śluzowych narządów płciowych. W zakresie tej ostatniej lokalizacji, klinicznie obserwuje się najczęściej występowanie ogniskowego zaniku błony śluzowej. Wykwitom mogą towarzyszyć objawy subiektywne jak świąd, ból, pieczenie. Schorzenie zdecydowanie częściej występuje u płci żeńskiej. Etiologia nie jest do końca poznana. Pod uwagę bierze się rolę czynników genetycznych, autoimmunologicznych, infekcyjnych, hormonalnych. Ważne jest wczesne rozpoznanie choroby i włączenie odpowiedniego leczenia, celem uniknięcia powikłań. W pracy przeprowadzono analizę dostępnego piśmiennictwa dotyczącego leczenia tej jednostki chorobowej.

Słowa kluczowe: **liszaj twardzinowy** / **narządy płciowe** / **leczenie** /

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Lichen sclerosus (lichen sclerosus, LS) is a chronic disease occurring mainly in women. The disorder has two peak ages of presentation: in the fifth and sixth decade of life and in the pre-puberty period [1]. It occurs less often in Black ethnic groups. The entity was first described by Hallopeau in 1889, while the historical description was reported in 1892 by Darier [2]. Due to the interdisciplinary nature of the disease, the exact incidence of the disease is unclear. It is estimated that in the general population the incidence is 1:300 (0.03%) to 1:1000 (0.1%). It occurs much more frequently in females, except during the pre-puberty period [3].

Lesions can occur in any location, but mostly affect the side surfaces of the neck, the collarbone area, arms, anterior surface of the chest, sub mammary regions and the flexion surfaces of the forearms. Typical lesions are porcelain-white papules that coalesce into larger plaques with the diameter of approximately 1 cm^2. A lilac ring may also be an additional sign. Older lesions are atrophied. Cases of epidermolysis in the bladder region have been reported [4]. Few cases of nails and oral mucous membrane involvement have been reported in literature as well [5].

The lesions may also affect the anogenital area. It is estimated that LS is the most common non-cancerous disease of the vulva epithelial**.** Its occurrence is estimated at 1 in 500 women of all ages, approximately [2]. The lesions occur within the labia majora and minora, clitoris and the anal area. LS is initially characterized by swelling of the vulva, which later transforms into a hardening associated with chronic inflammation. The elasticity of the skin decreases; labia minora and the clitoris recede. The lesions generally become white in color. As a result, gradual decay and accompanying scarring may lead to adhesions and strictures, causing dysuria and dyspareunia. Patients, especially elderly women, may have additional visible cracks, rifts, telangiectasia and bleeding. There is a condition known as perianal pyramidal protrusion, which is a variant of LS, occurring in female infants, consisting of lumps in between the crotch and the perianal area [6]. Erosions and ecchymosis in minors may be mistaken as the evidence of sexual abuse. Lesions are accompanied by intense itching and pain. These are the most common reasons why patients seek medical advice [3].

The diagnosis in most patients is usually made clinically, but a confirmatory biopsy remains a gold standard in cases with clinical doubt. It is helpful to exclude precancerous changes and cancer. Histological features include a thinned epidermis with focal hyperkeratosis, lymphocytic infiltrate and extended hyalinization in the upper dermis, homogenization of collagen and arteritis obliterans [7].

The etiology of the disease remains unknown. Genetic factors are thought to play a part in the development of the disease due to the presence of family cases, as well as determination of specific histocompatibility antigen HLA class II. HLA DQ7 antigen is found more often in girls and adult females with LS than in the control group. It seems that the immunological mechanisms play an important role in the pathogenesis of LS. A higher incidence of other autoimmune diseases such as diabetes, Graves-Basedow disease and alopecia areata has been reported in LS patients and their families. Autoimmune background of the disease may be confirmed by the detection of circulating autoantibodies against extracellular matrix protein type 1 or by targeting one of the pemphigoid antigens – BP 180, in the serum of patients with LS [8]. Since 1987, infectious agents such as Borrelia burgdorferi, Borrelia garinii and Borrelia afzelii were considered to be a factor in the pathogenesis of localized scleroderma and LS. However, consistent data has not fully confirmed the spirochete as a causative agent but since treatment with antibiotics such as penicillin and cephalosporin brings good results, this remains a matter of interest. The importance of hormonal factors was also not clearly explained. The disease has not been associated with pregnancy, hysterectomy, contraceptive or hormone replacement therapy although higher incidence of LS is observed in the group of postmenopausal women and prepubescent girls [3]. Interestingly, in the latter spontaneous remission is seen during adolescence. The regression of the anogenital area lesions is observed in an approximately 6% of females [9].

External factors play a role in the pathogenesis [10]. Chronic stimulation is thought to be a factor predisposing to the development of squamous cell carcinoma on the background of LS [11, 12]. Some authors suggest that LS is a special, superficial form of localized scleroderma. A similarity of LS and lichen planus, especially with regard to location, including genital mucosa, has also been suggested [13, 14]. However, LS distinct histological picture, including thinning live layers of the epidermis and degradation of the elastic fibers, are the distinguishing features. Additionally, in contrast to localized scleroderma, the continuity of the basement membrane is not maintained in LS [15].

The aim of the treatment is to reduce inflammation, prevent the formation of anatomical abnormalities and the development of malignant changes. Unfortunately, there is no effective therapy for LS. Potent or very potent **topical corticosteroids (GKS)** continue to occupy a prominent place in local therapy and remain the first-line treatment. In many studies, the topical use of potent GKS, such as clobetasol propionate, proved to be an effective treatment for LS in the clinical assessment. In the study of Bracco et al., it was more effective than a placebo and there were no adverse effects (i.e. infection, progression of atrophy, contact dermatitis) [16]. Furthermore, there was also a significant improvement in histological examination, including the reduction of inflammation [17]. In turn, men were tested using mometasone, which proved to be more effective than a placebo, too. In this study, mometasone was used at a concentration of 0.05%, while the commercially available one contains a concentration of 0.1%, which may signify that the effectiveness of the drug in the study was actually underestimated [18].

British Association of Dermatology Guidelines for the management of the disease recommend the use of very potent GKS in ointments or creams as first-line therapy [19]. Powell et al., recommend starting therapy using clobetasol at a concentration of 0.05% twice a day for 1 month and to continue treatment for another 2 months with one application in the evening. In order to avoid recurrence of the lesions, it is recommended to use potent steroids 1-2 times per week [20]. Lagos et al. propose to start the treatment with the application of clobetasol every night for one month, then every other day for another month. In the third month, the authors recommend the use of the product 2 times a week. In case of recurrence of the lesions it is proposed to return to the previous scheme at which improvement of the dermatological status was observed [21]. Based on the evaluation of clinical symptoms, improvement in skin condition and reduction of subjective symptoms were seen after topical

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tramcinolon application [22]. Quick resolution of the lesions is observed after an intralesional injection of tramcinolon at a concentration of 2.5-5 mg/ml. Local anesthetics are used in these cases. Such injections are often burdened with the possibility of adverse events, particularly the severity of an existing atrophy [23, 24].

An alternative treatment for GKS are **topical calcineurin inhibitors**. A study conducted by a Korean team has shown high efficacy and safety of topical tacrolimus, used twice a day, in the long-term therapy of LS [25, 26]. In another study, pimecrolimus, which proved to be equally effective, has been applied for two months. The majority of patients had partial or complete resolution of symptoms. Additionally, histological examination showed a decrease in inflammatory infiltration and expression of molecules CD3 (+), CD8 (+), CD57 (+) T cells [27]. Subsequent studies have shown an increased expression of p53 and reduction of protein Bcl - 2 particles in the keratinocytes of basal layer during pimecrolimus treatment [28]. Goldstein et al. compared the clinical efficacy of pimecrolimus and clobetasol propionate and found no differences in this respect. It should be noted that in that study clobetasol was used only once a day. Moreover, the histological examination showed favorable results with respect to clobetasol rather than pimecrolimus. There were no adverse effects of the above-mentioned drugs [29].

It is worth noting that pimecrolimus is a substance approved for use in atopic dermatitis and its recommendation to a patient with LS is an off label procedure. One should always bear in mind the contraindications for the use of immunosuppressive drugs in patients with LS co-infected with Human Papilloma Virus (HPV), due to an increased risk of developing malignancies [30, 31]. Especially since studies on the effectiveness of individual drugs in the LS include periods not longer than one year, which is undoubtedly an insufficient amount of time to evaluate future adverse effects. Drugs derived from vitamin A, such as **isotretynoin**, may be used in cases when other topical treatments have no effect, but skin irritation may limit their use [32, 33].

In the past it was recommended to use ointments and creams containing **hormones**: testosterone, progesterone, estrogen, but the effects were not satisfactory. Testosterone ointment showed efficacy of the placebo [16]. In addition, topical testosterone can lead to virilization [34].

Taking into account the unknown infectious agent in the pathogenesis of LS, the possibility of using **antibiotics** should be mentioned. The results show some efficacy of **penicillins** and **cephalosporins**. An improvement in the clinical status and reduction of symptoms after using these drugs in intramuscular injection or by oral administration was noted. However, blind, randomized studies and controlled trials were never performed [35]. Another drug that tends to be effective is **acitretin**, a synthetic analogue of retinoic acid which reduces hyperkeratosis and normalizes the renewal and differentiation of epidermal cells. Taking 20-30 mg of the drug daily for 16 weeks has been proven to significantly improve the clinical status of patients. The study made no placebo control [32].

According to Baskan et al. the use of medium doses (3-4 mg/kg) of **cyclosporin** for 3 months offers an alternative for resistant LS. After the therapy, clinical improvement was observed but histological examination was not performed due to the lack of consent from the patients [36].

In 2002, reports were published on the efficacy of UVA **phototherapy** using a cream with **psoralens** in patients with inflammatory diseases of the anogenital area, including the LS. Most patients showed improvement in the clinical status and reduction in itching. However, the potential increased risk of malignancies may limit its use [37]. There are also isolated reports of successful therapies with **stanazol**, **hydroxychloroquine**, and **calcitriol**, which also did not include the placebo group [38, 39].

In the literature, results of studies evaluating the effectiveness of **CO_2 laser** treatment have been found. Unfortunately, this method requires hospitalization and sometimes is performed under general anesthesia [40]. Based on the results of clinical observations, a **photodynamic therapy** has proven to be an effective treatment in vulvar LS, especially when it comes to reduction or complete relief of symptoms reported by patients. In addition, immunohistochemical and histological studies showed a reduction in inflammatory infiltrate in the tissue [41, 42]. Eventually, if the disease has a tendency to progress and there is no response to treatment, surgical treatment may be used to correct anatomical changes caused by the disease [43]. However, it should be noted that even after applying **surgical methods,** a recurrence is observed in as many as 85% of cases [44].

It is also important to instruct patients about proper hygiene. Cleaning agents with acidic pH, detergent-, dye- and fragrance-free, should be used. The anogenital area should be very thoroughly dried. Colored and perfumed toilet paper, panty liners and tampons should not be used. Underwear should be white, cotton and not too tight. Also, patients should be discouraged from mechanical stimulation of the affected area, such as shaving [45].

In case when the prescribed therapy fails, other factors such as coexisting candidiasis of the vulva, incorrect diagnosis (cancer, psoriasis, mucous membrane pemphigoid) and non-compliance (e.g., due to fear of adverse reaction of GKS) should be considered [34]).

Until recently, the goal of the LS treatment was believed to be an improvement of the quality of life for the patient by reducing the symptoms such as pain, itching and burning. Currently, an increased focus is put on the possibility of a malignant transformation. The risk of developing squamous cell carcinoma (SCC) on the ground of LS ranges from 4 to 5%, while the incidence of the primary SCC in the UK population is 0.3% [20, 46]. There are also descriptions of vulvar verrucous carcinoma in women with LS [47].

The choice of the proper method of treatment continues to present the greatest challenge, keeping in mind that therapy can result in an uncontrolled emergence of adverse effects and may intensify the existing disorders, including atrophy. Both gynecologists and dermatologists should be involved in the process of treatment, as sometimes the lesions within the genital mucosa should be differentiated from many other dermatoses. Topical, potent GKS remain the first-line treatment.

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