REVIEW

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Anogenital Lichen Sclerosus: Clinical Considerations and Management

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ABSTRACT

Lichen sclerosus (LS) is a chronic inflammatory disease, which commonly involves anogenital region. It may cause significant functional and cosmetic problems and may show malignant transformation. Treatment modalities change according to the age of the patient, severity and duration of the lesions. In this review, the clinically important aspects of anogential LS and its treatment will be discussed.

Keywords: Balanitis, Dyspareunia, Dysuria, Fissures, Genital, Premalignant, Squamous cell carcinoma, Vulvar disease, Vulvar dermatosis

Introduction

Lichen sclerosus (LS) is a chronic inflammatory disease of unknown etiology that commonly involves anogenital region. It can severely impact quality of life by causing severe functional and cosmetic problems. Anogenital LS may show malignant transformation. Extragenital manifestations may occur, however they do not cause functional impairment most of the time and do not have a risk of malignant transformation. In this review, we will discuss clinical features and treatment options of anogenital LS.

Epidemiology

In general gynecology practice, vulvar LS prevalence of 1.7% was reported [1]. Examination of 96 elderly women who were nursing home residents revealed that 3% of them had genital LS. This high rate may be attributed to age, immobilization and incontinence [2]. An increasing incidence of premenarchal genital LS was observed, with an estimated prevalence of 1 in 900 [3]. Male genital LS is probably an under-recognized and under-reported condition. Studies have shown that one-third of adult male genital LS patients had a delay of at least two years before the definitive diagnosis was established [4,5]. A United States based electronic medical record revealed an incidence of 1.4 male genital LS cases per 100,000 visits [6]. Epidemiology of the disease may vary between countries as the condition has a propensity to occur in uncircumcised men. Males with a history of neonatal circumcision are unequivocally spared from the disease [5].

Etiology

Several factors including genetic factors, autoimmunity, hormonal factors, infections and drugs have been suspected, which are beyond the scope of this review. However, as they are important from clinical point of view, chronic irritation and trauma (Koebnerization) will be briefly discussed. The chronic contact with urine has been implicated in the development of LS [5,7,8]. Cases of vulvar LS have been reported in association with urinary incontinence and, in some cases, lesions resolved following treatment of urinary incontinence [9]. As mentioned above, LS do not occur in neonatally circumcised males and urinary dribbling is a frequent finding in male patients

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with genital LS. Thus, it is likely that the moist and occlusive environment under the prepuce contributes to the pathogenesis of LS. In men, lesions of LS spare almost invariably the perianal region, which does not come into contact with urine [5,8]. No difference was found in urinary constituents of males with and without genital LS [10].

Genital LS may also occur following trauma, such as surgery, instrumentation and at sites of genital jewelries, and recurs in circumcision scars and grafts [7,8].

Clinical Features

Adult Female Anogenital Lichen Sclerosus

About 60% with women with anogenital LS are symptomatic. However, this ratio reaches 100% in patients who are referred to specialists [11]. Cardinal symptom of the disease is pruritus, which is frequently severe, often aggravates at night and may lead to sleep disturbances [7,11,12]. Erosions and fissures may lead to pain, soreness, dysuria, urinary retention and dyspareunia [7,12,13]. Sexual dysfunctions including dyspareunia, decreased frequency of intercourse, apereunia and difficulty achieving orgasm were reported and may also result from anatomical changes such as stenosis of the introitus [14]. Perianal stenosis may lead to pain during defecation [15]. Comprehensive list of symptoms associated with anogenital LS in women can be found in Table 1.

Early findings of the adult female anogenital LS include a well-demarcated, slightly erythematous plaque and edema at the periclitoral hood [7,16]. Porcelain white papules and plaques are characteristic lesions of the disease, that are often accompanied by ecchymoses [12]. Follicular delling and hyperkeratosis may be seen [7,12]. Fissuring is another important feature, that tends to occur in the area between clitoris and urethra, interlabial sulci and the base of posterior fourchette [7,16]. Ulcerations, erosions and rarely blisters may be seen [15]. Due to chronic scratching, some patients may exhibit accompanying subepithelial hemorrhage and lichen simplex chronicus lesions [7]. Long-lasting disease leads to hypopigmentation, sclerosis and atrophy of the skin, termed as cellophane paper-like appearance [7]. Scarring may eventually result in partial or complete resorption of the labia minora, burring of the clitoris and sealing of the clitoral hood [7,12]. Pseudocyst smegmatis may develop due to adhesions of the clitoral hood [17]. Any persistent ulcerated and/or hyperkeratotic firm lesion on vulva should raise a suspicion of squamous cell carcinoma (SCC) [17]. Basal cell carcinoma and Merkel cell carcinoma have been reported, which were probably co-incidental [13]. Pigmented lesions, most commonly lentigines and melanocytic nevi, may also arise in vulvar LS lesions [17,18]. Genital melanocytic nevi associated with LS display severe histopathological atypia and may mimic melanoma [18]. Vulvar melanoma has rarely been reported [18].

The extent of involvement in female anogenital LS may vary considerably. In some patients the disease may be restricted to a small, focal area; while in others it may cover the entire vulva, perineum and perianal region [7]. Labia minora, interlabial sulci, clitoris, clitoral hood and perineal body are the typical regions affected in adult females with anogenital LS. Perianal involvement has been reported in 30% of the patients (Figure 1). Genital LS affecting vulvar, perineal and anal areas gives rise to "figure-of-eight" shape, also termed as "keyhole" or "hourglass" appearance [19]. In extensive cases, lesions may involve gluteal region and genitocrural folds [12]. In contrast to lichen planus, the vagina and cervix are unlikely to be involved in LS [12]. There are rare cases of LS that have been reported to affect the vagina, most of which had associated pelvic organ prolapse [20,21,22]. Concerning the latter cases, it is hypothesized that the metaplasia of the vaginal epithelium due to chronic irritation might have led to the development of LS on the vaginal mucosa [22].

Table 1. Symptoms of anogenital lichen sclerosus in women

Itching
Pain, soreness, burning sensation
Hemorrhage
Dysuria, urethral discharge, poor urinary stream
Dyspareunia, apareunia, decreased frequency of intercourse, difficulty achieving orgasm
Vaginal discharge
Changing anatomy of the genitalia
Pain during defecation, constipation, stool holding, rectorrhagia
Sleep disturbances

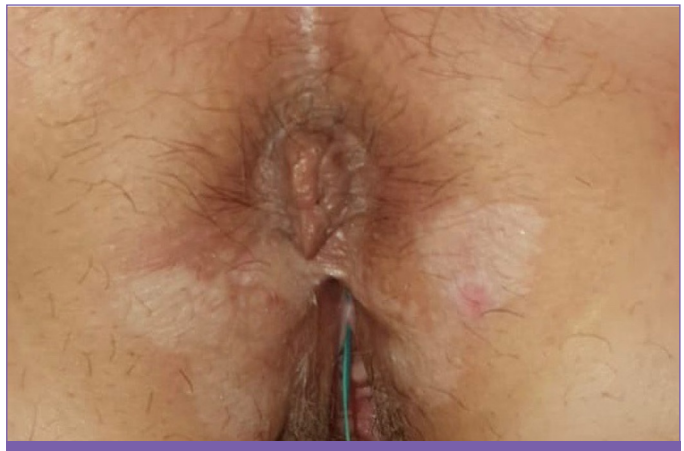

Figure 1. Genital lichen sclerosus in a postmenopausal woman. Porcelain white plaques involving perianal region can be seen. Authors declare patient consent was obtained for clinical photographs

Child Female Anogenital Lichen Sclerosus

The symptoms and clinical features of child female anogenital LS are generally similar to those observed in adult females (Figure 2,3) [12].

However, there are several differences that are worth mentioning. Behavioral problems, urinary symptoms and constipation are more frequently observed in children [23]. Clinically, the ecchymoses and purpura may be very prominent in children, and may be confused with sexual abuse [7]. In addition, infantile perineal protrusion (IPP) is a finding that occurs almost always in prepubertal girls. Formerly termed as "infantile perianal pyramidal protrusion", IPP a soft tissue protrusion most commonly located anterior to anus. The condition may occur concomitantly with LS or may precede the latter [24]. Cases of labial fusion, defined as partial or complete adherence of labia minora in the midline, have been reported in association with LS [25].

Similar to adults, vulvar melanocytic nevi may be superimposed on LS lesions in children [18,26,27]. Rare cases of vulvar melanoma have been reported in children in association with LS [28,29,30]. However, it is postulated that some of the latter cases may possibly represent melanocytic nevi misdiagnosed as melanoma [26].

Clinical features of female anogenital LS are summarized in Table 2.

Adult Male Genital Lichen Sclerosus

Most common symptoms of male genital LS include dyspareunia and urological symptoms such as impaired urinary flow. Burning and itching sensation may occur [5,31]. A comprehensive list of symptoms associated with male genital LS can be found in Table 3.

Male genital LS is mostly a clinical diagnosis [5]. Typical sites of involvement are the foreskin and glans penis [5,31]. Loss of coronal sulcus anatomy, hypopigmented patches and plaques, bullae, ulcerations and erosions can be observed [5]. Sclerotic plaques and bands lead to the tightening of the prepuce, termed as constrictive sclerotic posthitis, which may result in the development of paraphimosis and phimosis [5,12]. Ring-like constriction, also termed as pseudo-ainhum, has been reported at the penile shaft [32]. Meatal and urethral disease, varying from isolated meatal to panurethral involvement may occur [12,31]. High rates of urethral involvement, affecting 20% of the patients, were reported in urological literature [33]. Scarring of the meatal area may lead to stenosis and obstruction [12]. Unlike female genital LS, perianal LS is very unusual in men [5]. New-onset indurations arising on LS lesions should be biopsied to rule out SCC [34]. Benign pigmented lesions, namely postinflammatory hyperpigmentation, lentigines and melanocytic nevi, may co-exist with LS on glans and prepuce [27,35,36]. Penile melanoma, an extremely rare entity, was reported to develop on LS lesions in three adult males [37].

Child Male Genital Lichen Sclerosis

Phimosis is the most common presentation of child male genital LS, followed by balanitis and buried penis [38]. Of note, LS is the most frequent cause of acquired phimosis in boys [17]. Perianal involvement is very rare, as in adult men [7,12].

Clinical features of male genital LS are summarized in Table 4.

Differential Diagnosis

Differential diagnosis of genital LS in adults include lichenoid disorders such as lichen planus, lichen simplex chronicus, and contact dermatitis. In children with genital LS, vitiligo is the major differential diagnosis. Wood's lamp examination may be helpful in

Table 2. Clinical features of female anogenital lichen sclerosus

Well-demarcated erythematous plaques (early finding)
Edema, especially of the periclitoral hood (early finding)
Porcelain white papules and plaques (typical)
Purpura and ecchymoses (more prominent in children)
Follicular delling
Hyperkeratosis
Fissures (between clitoris and urethra, at interlabial sulci, at the base of posterior fourchette)
Ulcerations, erosions
Blisters (rare)
Sclerosis and hypopigmentation
Atrophy of the skin (also termed as cellophane paper-like appearance) (late finding)
Resorption of the labia minora (late finding)
Burring of the clitoris and sealing of the clitoral hood (late finding)
Stenosis of introitus and perianal region (late finding)
Pseudocyst smegmatis (late finding)
Vulvar squamous cell carcinoma, rarely basal cell carcinoma and Merkel cell carcinoma (only in adults)
Vulvar pigmented lesions (lentigines, melanocytic nevi, very rarely melanoma)
Infantile perineal protrusion (only in children)
Labial fusion (only in children)

Table 3. Symptoms of adult male genital lichen sclerosus

Dyspareunia due to painful erection, fissuring during and after sexual intercourse
Dysuria, poor urinary stream with decreased flow and diameter
Dribbling
Difficulty retracting foreskin
Soreness, burning
Itching
Change in the appearance of genitalia
Brusing, bleeding
Erosions, ulcers, blisters

this picture. Another important differential diagnosis that should be kept in mind in child age group is child abuse. Patients should be carefully inspected in this respect. In cases with hyperplastic changes in histopathology, malignancies should be ruled out.

Treatment

The treatment of LS is consituted of many alternatives and has many perspectives. The contact of irritants should be minimized, urinary contact should be avoided and soaps should be substituted with sydnets. Any possible infection should be treated with effective antibiotherapy and the use of emollients should be made routine. Ultrapotent or potent topical corticosteroids are first line for the treatment of the lesions. In steroid-resistant cases, calcineurin inhibitors, topical retinoids, systemic retinoids, systemic immunosuppression phototherapy, photodynamic therapy are the alternatives. The patients should be under surveillance for squamous intraepithelial neoplasia or cancer; and biopsy should be performed in case of suspicion. The three broad categories of general measures, treatment and surveillance are summarized in Table 5 [7,39].

Table 4. Clinical features of male genital lichen sclerosus

Constrictive sclerotic posthitis
Balanitis
Sclerosis of the glans
Loss of coronal sulcus
Pseudo-ainhum of the penis
Meatal stenosis
Hypopigmented patches
Purpura, telangiectasias, petechiae
Bullae, erosions, ulcerations
Penile squamous cell carcinoma, erythroplasia of Queyrat, verrucous carcinoma
Penile pigmented lesions (lentigines, melanocytic nevi, very rarely melanoma)

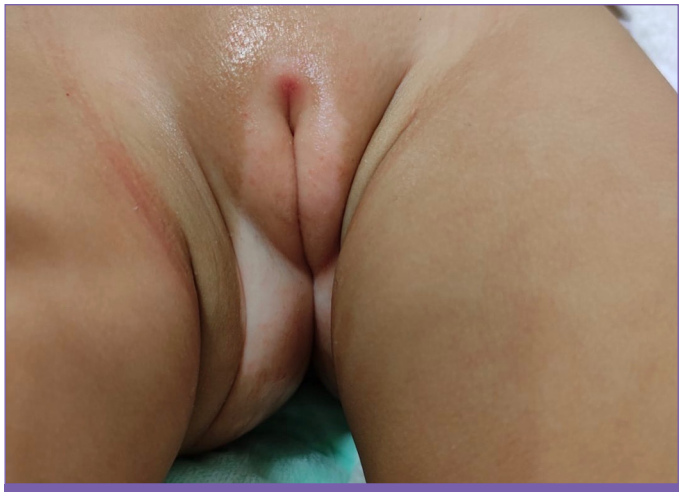

Figure 2. Genital lichen sclerosus in a prepubertal girl. Note the sclerotic white plaques and erosion. Authors declare patient consent was obtained for clinical photographs

Treatment Strategies According to Gender

Ultrapotent and potent topical corticosteroids are the first line treatment for females with genital LS; with greater efficacy than the other treatment alternatives. Complete cure should not be aimed rather the relief of the symptoms is achieved in 75 to 95% of the cases. In male patients with genital LS circumcision is the most effective treatment modality. However, the use of ultrapotent and potent topical corticosteroids should be offered initially for three months. Table 6 summarizes previously reported effective treatment modalities in the literature according to gender [40].

Topical Steroids

Potent topical steroids (eg. Clobetasol propionate 0.05%) are the first line in the treatment of genital LS both in female and male patients [7,40,41]. The use of topical steroids should be combined

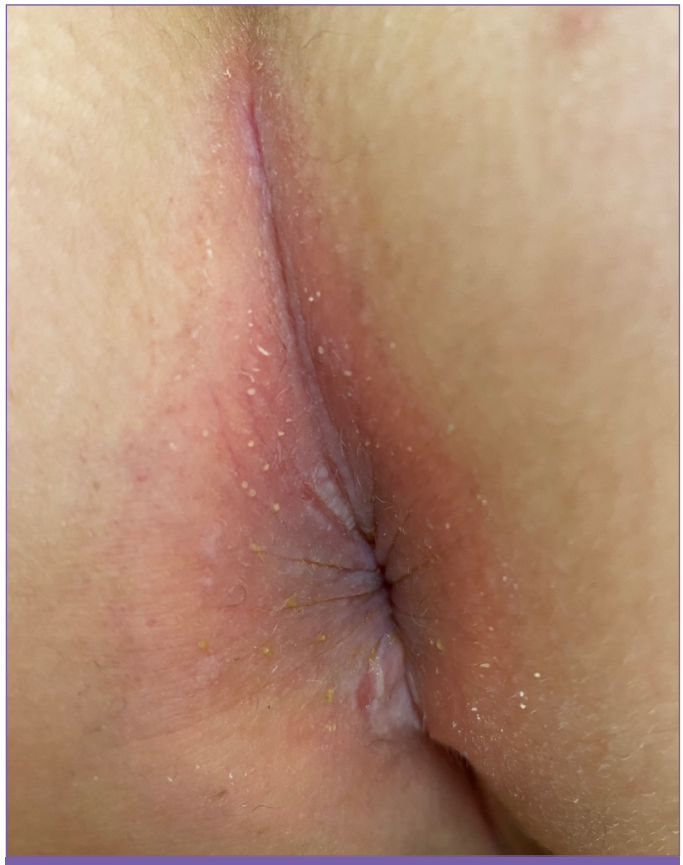

Figure 3. Perianal involvement of lichen sclerosus in a prepubertal girl. Note the erythema, sclerosis, fissures (intergluteal and perianal) and erosions. Authors declare patient consent was obtained for clinical photographs

with the soap substitution and the use of emollients [12]. The initially recommended treatment frequency and duration vary from once to twice daily and one to three months in different guidelines [7,12,40]. The European guideline recommends the use of topical corticosteroids twice daily in the first month of treatment and then decreasing the frequency to once daily in milder cases [40]. The British guideline recommendations differ according to gender. Female patients are recommended to use topical clobetasol propionate 0.05% once daily for the first month, alternative days in the second month and two to three times a day in the third month. Male patients are recommended to use topical clobetasol propionate 0.05% once daily for one to three months. The intralesional injection of triamcinolone acetonide is recommended in both genders in case of hyperkeratotic lesion given that malignancy has been excluded [12]. The usual amount to be used in each application is a fingertip unit; with a maximum of 10 g per month in order to avoid the steroid side affects such as epidermal atrophy and telangiectasias [40].

After the initial one to three months treatment with potent topical corticosteroids, maintenance treatment with either topical steroids or topical calcineurine inhibitors is recommended in order to prevent relapses [7,12,40]. The frequency of maintenance treatment to successfully remain lesion free varies according to each patient; some patients require once to twice monthly uses whereas others require once to twice weekly. The proactive application of one or twice weekly mid potency topical corticosteroids (eg, mometasone furoate 0.1%) was proven to be effective in maintenance treatment. A maximum of 30 g per 3 months topical corticosteroid use is recommended in maintenance in order to prevent the side effects of long-term topical corticosteroid use [40].

The use of ultrapotent topical corticosteroids (e.g., betamethasone dipropionate 0.05%, diflorasone diacetate 0.05% and clobetasol propionate 0.05%) twice daily for six to eight weeks is also the mainstay treatment in pediatric LS patients with minimal side effects. While mid potency topical corticosteroids such as (triamcinolone acetonide and mometasone furoate) have also been found to be effective, their use in pediatric LS cases is not first line [39].

Topical Calcineurin Inhibitors

The topical calcineurin inhibitors are the second-line treatment options in genital LS patients in whom topical glucocorticoids are non-responsive or not tolerated [42]. Topical calcineurin inhibitors may be used in the maintenance of lichen scleroatrophicus after an initial three months treatment with potent corticosteroids [7,40].

Topical pimecrolimus 1% cream is recommended to be used twice daily up to six months in genital LS patients [7]. Compared to clobetasol propionate 0.05% cream applied once daily, pimecrolimus 1% cream twice daily is less effective in the treatment of genital lichen scleroathrophicus [43]. Topical tacrolimus was used in its 0.1% preperation in most of the studies. Tacrolimus (0.1%)

Table 5. General treatment perspective of LS

General measures	Treatment	Surveillance
Avoid the contact of urine	1st line: Ultrapotent or potent topical corticosteriods	Follow-up for squamous intraepithelial neoplasia and cancer
Use of syndets instead of soaps		
Minimising the contact of irritants	Topical calcineurin inhibitors, retinoids, phototherapy, photodynamic treatment, systemic immunosupresion and circumsion for resistant cases	
Use of emollients		Biopsy if any suspicion

Table 6. Effective treatment modalities according to gender [40]

Female	Male
Topical steroids	Topical steroids
Intralesional steroids	Topical tacrolimus (0.03% and 0.1%)
Topical testosterone (2%)	Pimecrolimus (1%)
Topical progesterone (2% and 8%)	Circumcision
Cyclosporine	
Topical tacrolimus (0.03% and 0.1%)	
Pimecrolimus (1%)	
Retinoids	
Oxatomide	
Carbondioxide laser	
Perineotomy	

ointment is recommended twice daily for three months in patients with genital LS [7]. There is also a case of steroid-resistant genital LS which was successfully treated with tacrolimus 0.03% ointment [44]. Tacrolimus 0.03% ointment was shown to be effective and safe for the treatment of pediatric genital LS [45].

Phototherapy

Beattie et al. [46] investigated the treatment efficacy of ultraviolet-A-1 (UVA1) phototherapy in corticosteroid-resistant genital LS in seven female patients. Five of the patients achieved complete remission after treatment. UVA1 phototherapy is of benefit in the management of resistant vulvar LS cases [46]. Garrido-Colmenero et al. [47] recently reported a vulvar LS case that was successfully treated with narrowband ultraviolet-B, which was resistant to topical steroids, twice weekly, at a dose of 0.2 j/cm^2 for 5 months.

Circumcision

Circumcision is a treatment option for LS as well. The male genital LS patients who have not responded to a three months course of topical potent steroid treatment should be re-evaluated for the possiblities of phymosis, paraphymosis and burried penis (due to obesity) which would with old the application of topical steroids. Obese patients should be encouraged for weight loss. Patients with phymosis or paraphymosis should be referred to urology for circumcision. Circumcision may be considered in patients not responding to topical steroids as well [12]. Uretheroplasty or meatoplasty may be necessary in cases of extensive stenosis. Topical corticosteroids are recommended to be applied in the postsurgical period as well [48]. Nevertheless, it should be kept in mind that there is still the risk of squamous neoplasia development even in early-circumcised male genital LS patients [49].

Topical Testosterone

Testosterone, in a topical preparation of 2%, was used in the treatment of vulvar LS in several studies. Yet it is effective in the palliation of symptoms, Ayhan et al. [50] have shown that topical testosterone (2%) is not as effective as topical clobetasol propionate (0.05%) in the initial and maintenance treatments of vulvar LS. Still, premenopausal patients respond better, have higher remission and lower response rates to topical androgens than the postmenopausal patients [50,51].

Photodynamic Treatment

Photodynamic treatment is a treatment modality in which 5% 5-aminolevulinic acid is applied to the treatment area that is subsequently irradiated with a halogenic lamp (wavelenght of 590-760 nm) for 10 minutes. It is a beneficial treatment modality for vulvar LS. The greatest treatment benefit is seen in the reduction of subepithelial ecchymoses, telangiectasias, erosions and fissures. It has limited benefit in the atrophic lesions. Overall, it is a safe treatment alternative that promises good results in the treatment of vulvar LS [52,53].

Laser

Laser modalities are utilized in many different diagnoses. Recently, the use of non-ablative lasers in the treatment of vulvar LS has been investigated by Bizjak Ogrinc et al. [54] Nd: Yittrium Aluminium Garment Laser, R33 headpiece, was used with a spot size of 9 mm and a fluence of 90 j/cm^2. The patients received 3 sessions of laser treatment with 14 days intervals along with topical corticosteroids. Compared to the corticosteroid-only group, the combination of topical corticosteroid and laser led to greater reduction in burning, itching, pain, dyspareunia and sclerosis with minimal patient discomfort and maximal patient satisfaction [54]. Fractionated carbon dioxide laser may be used in the treatment of refractive vulvar LS cases as well. In a study by Balchander and Nyirjesy [55], patients received at least two sessions of laser treatment with at least monthly intervals. Two months after the last treatment session, patients reported a significant reduction in dysuria, dyspareunia, itching and vaginal pain as well as a reduction in the use of topical corticosteroids. Thus, fractionated carbon dioxide laser may be a treatment alternative in resistant cases [55].

Adalimumab

Similar to other inflammatory dermatoses, tumor necrosis factor-alpha (TNF-alpha) levels are high in LS. Adalimumab is a monoclonal anti-TNF-alpha antibody which is used in the treatment of inflammatory dermatoses. A patient with balanitis xerotica obliterans, refractive to treatment with topical steroids and topical calcineurin inhibitors, was treated with intralesional 40 mg adalimumab injections with two weeks interval for six months. Although the patient benefited from treatment, injections were painful and expensive. Relapse occurred eight weeks after treatment cessation. Nonetheless, anti-TNF agents are promising modalities for LS in the future [56].

Topical and Systemic Retinoids

There are many reports of topical and systemic retinoid use in female lichen sclerosis. Topical 0.025% tretinoin 5 days a week for one year and acitretin 20-30 mg/day for twelve weeks were both effective in the treatment of genital lichen sclerosis in women. Side effects of retinoid use were observed [57,58]. Only one study was perfomed in male genital lichen sclerosis patients, 35 mg/day acitretin was given for twenty weeks. Acitretin was found to be effective in the treatment of balanitis xerotica obliterans with tolerable side effects [59].

Cyclosporine

Cyclosporine is also a treatment alternative in refractory LS patients. Bulbul Baskan et al. [60] treated five refractory female genital LS patients with oral cyclosporine for three months with doses ranging from 3 to 4 mg/kg/day. Erythema and erosions improved significantly and the total symptom scores regressed. Patients experienced mild adverse effects such as nausea, hypertrichosis and mucositis. Oral cyclosporine is a safe and effective treatment alternative in vulvar LS patients refractory to treatment [60].

Prognosis

Prognosis of Vulvar Lichen Sclerosis

Cooper et al. [61] analysed 327 female genital LS patients with definitive histopathological diagnosis. Of these patients, 255 responded to the initial treatment of topical corticosteroids, 244 (96%) with improvement in symptoms, 168 (66%) symptom free, 76 (30%) partial response and 11 (4%) poor response. SCC has developed in 6 (2.4%) patients and scarring was significantly less often in girls. The lifelong remission rate of vulvar lichen sclerosis was 16% [61]. According to Bradford and Fischer [62], symptom remission due to topical corticosteroids is achieved in 98% of the compliant and 75% of the non-compliant patients. Progression with scarring was not observed in any of the compliant patients but in 35% of the non-compliant patients. None of the compliant patients developed squamous cell cancer; on the other hand five of the non-compliant patients developed SCC, which is statistically significant. Mild corticosteroid side effects were seen in 7% of the patients in the long-term follow-up. According to the authors, topical corticosteroid treatment has a protective effect against sclerosis and the development of squamous cell cancer in female lichen sclerosis patients [62].

SCC is the most important complication of vulvar lichen sclerosis. The risk of SCC arising from lichen sclerosis is 5%. The SCC arising within vulvar lichen sclerosis lesions arises within well-differentiated type vulvar intraepithelial neoplasia. If SCC is to arise in the background of vulvar lichen sclerosis, it becomes invasive within six months. The risk of SCC development within the vulvar LS lesion depends on the duration and severity of LS rather than the patient's age [63].

Prognosis of Balanitis Xerotica Obliterans

Nasca et al. [64] evaluated 86 male genital LS patients with a 10 years follow-up interval. Of these 86 patients, five had malignant transformation: three SCC, one erythroplasia of Queyrat and one verrucous carcinoma. The average lag time between the diagnosis of LS to malignant transformation was 17 years. Human papilloma virus (HPV) was present in four of these five patients. Thus, male patients with genital lichen sclerosis are at increased risk of malignant transformation and the risk is associated with HPV positivity [64]. Barbagli et al. [34] also reported a series of 130 male genital LS patients with 10 years follow-up. In their series, 11 (8.4%) of the patients showed malignant transformation: 7 (64%) SCC, 2 (18%) verrucous carcinoma, 1 (9%) erythroplasia of Queyrat and 1 (9%) SCC within verrucous carcinoma. Thus, long-term follow-up of male genital LS patients is mandatory [34].

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: M.Ç.O., T.K.U., Design: M.Ç.O., T.K.U., Data Collection or Processing: M.Ç.O., T.K.U., Analysis or Interpretation: T.K.U., Literature Search: M.Ç.O., D.Ö., Writing: M.Ç.O., D.Ö., T.K.U.

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