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Research Article

Lichen Sclerosis

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Abstract

Lichen sclerosis is a chronic inflammatory mucocutaneous condition involving anogenital areas affecting women of all ages predominantly postmenopausal women. Lichen sclerosis is associated with risk factors like frequent trauma, hormonal status, autoimmune diseases and infections but the etiology is still not known. It clinically presents as chronic white atrophic patches with soreness and itching in the perianal, vulval and penile regions; also genital scarring and sexual and urinary dysfunction may be seen and may even lead to squamous cell carcinoma. It is clinically diagnosed and skin biopsy can also be done. The treatment modalities include corticosteroids, topical calcineurin inhibitors like pimecrolimus and tacrolimus. Potential of non steroidal treatment like Platelet rich plasma therapy, HIFU (high intensity focused ultrasound), UV light treatment, energy based modalities like CO2 lasers, surgical measures have also been investigated. In this article an update about clinical features, pathogenesis, diagnosis and emerging treatment options have been provided.

Keywords

Lichen sclerosis, autoimmune, CO2 lasers, atrophy, corticosteroids.

INTRODUCTION

Lichen sclerosis is a chronic, inflammatory mucocutaneous immune mediated disease mainly affecting the anogenital areas. Lichen sclerosis is a disease affecting predominantly postmenopausal women but may also be found in adolescents, prepubertal children and men. Lichen sclerosis has familial and genetic predisposition and associated with factors like frequent trauma, hormonal status and drugs which may play a role in its pathogenesis but the etiology is still unknown. Genes related to tissue remodeling and oxidative stress may lead to scarring and malignancy [1]. Clinically LS in anogenital areas presents as ivory white patches, atrophy, severe pruritis progressing to scarring of vaginal introitus, phimosis and functional impairment affecting the quality of life [2]. Extragenital areas can be neck, shoulders, upper trunk, thighs and oral cavity [3,4]. Treatment includes use of corticosteroids, calineurin inhibitors, hormonal and other non hormonal treatment like LASER, HIFU, UV light treatments and surgical procedures [1,5]. To prevent complications early diagnosis, proper treatment and long term follow up is required [6].

Epidemiology

Lichen sclerosis can occur at any age and in both sexes. It is most commonly seen in females [6] due to low estrogen status leading to a humoral over T-cell mediated response and also leads to koebner phenomenon due to absence of proper lubrication [6]. It has a bimodal peak affecting one in prepubertal girls and the other in peri- and postmenopausal women. 54% of women were postmenopausal according to a study of Lichen sclerosis in general gynaecology practice [7].

Pathogenesis

(A) Genetics: - Lichen sclerosis is an autoimmune disorder with genetic component and a positive family history of LS in a first degree relative can be found in 12% of patients [8]. HLA-DQ7 is found to have significant association with LS [9-13].

(B) Epigenetic:- In LS epigenetic changes may significantly induce malignant transformation. LS is associated with alteration in isocitrate dehydrogenase which is an enzyme responsible for DNA 5-hydroxymethylation patterns. As a result, the overall methylation levels in the epidermis are diminished in LS and therefore UVA1 treatment can lead to normalization of these levels [14].

(C) Immunology:- In this there is T-cell infiltration limited to dermis consisting of CD8+ and Treg T-cells and CD4+ T-cells [15]. Frequently associated autoimmune diseases with LS in women include autoimmune thyroid disease (Hashimoto thyroiditis and Grave's disease), pernicious anemia, alopecia areata and vitiligo [16-19].

(D) Proliferation of Fibroblast:- In LS there is

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increased collagen synthesis in the dermis especially Collagen I and III which ultimately leads to downregulation of cell growth rate [20].

(E) Oxidative stress:- The pathogenesis, maintenance and progression of LS (a chronic inflammatory disease) occurs due to oxidative stress. Oxidative DNA damage leads to inactivation of tumour suppressor genes and downregulation of expression of cyclin dependent kinase inhibitors $p161^{INK4}$ and $p27^{Kipl}$ leading to cell proliferation and transformation of malignancy [13,21,22].

Risk Factors

(A) Local Factors:- Trauma and chronic irritation play an important part in LS like scratching, friction,sexual activity,occlusion and surgical procedures acting as Koebner phenomenon leading to LS lesions appearance [23]. Also multiparity, high BMI, urinary incontinence, infrequent genital washing in elderly women leads to LS [24].

(B) Hormonal Factors:- LS is associated with low estrogen levels and testosterone deficiency [25] due its bimodal presentation in prepubertal and postmenopausal women but it is still controversial.

(C) Infections:- Association has been found with HPV (Human Pappiloma Virus) [26,27], Hepatitis C Virus (HCV) [28,29], Borrelia burgdorferi (causative agent of Lyme's Disease) [30].

(D) Medicines:- Severe variants of LS seen in patients treated for CML and GIST with imatinib mesylate [31,32]. Carbamazepin intake for six months can also lead to LS [33]. An inverse relationship is seen between LS, beta blockers and ACE inhibitors [34].

Clinical Presentation

LS is an inflammatory, chronic, progressive, non-neoplastic epithelial disease affecting the perianal, perineal and genital labia. Extragenital involvement areas can be axillae, buttocks, thighs, upper trunk and oral mucosa rarely [35,36]. The lesions present as wax textured, glistening, ivory colored flat spots coalescing into thin or hyperkeratotic patches causing itching, burning sensation, redness swelling. Perianal region lesion may present as "figure of eight" also known as "keyhole" or "hourglass" shape lesion. Progression of disease can lead to scarring which is seen in many adult females and girls [5], skin cracks and bleeding causing painful sore areas with secondary infections. Scarring can cause vaginal introitus narrowing leading to coital difficulty, unsatisfactory sexual activity, depression and poor quality of life [37]. It may also cause anal stenosis, obstruction, urinary retention and constipation, IBS, thyroid dysfunction, vulvar pain [38]. Vulvar LS has 4-6.7% risk of Squamous cell carcinoma of vulva [39,40].

Diagnosis

The diagnosis of LS is clinical typically along with complete medical history and physical examination. Dermascopy is a non invasive method for diagnosis of LS and biopsy site optimisation [41]. Biopsy should be done in hyperkeratotic areas and erosions not improving with treatment or at the sites with altered pigmentation [42]. Further assessment should be done for autoimmune diseases like thyroid autoimmune diseases, scleroderma, type 1 diabetes mellitus and rheumatoid arthritis [43,44]. Proper and timely diagnosis with early treatment are helpful in preventing complications.

Differential Diagnosis

List of differential diagnosis includes candida vulvitis or thrush, postmenopausal atrophy, vitiligo, lichen planus, leukoplakia, psoriasis, scleroderma, pagets disease, mucous membranous pemphigoid, vulvar intraepithelial neoplasia and hence may lead to delay in diagnosis [45]. Sexual abuse should be ruled out in children with ecchymotic and bleeding lesions [43,46].

Management

All cases of LS should be treated to prevent scarring, anatomical, sexual and urinary dysfunction and also to sustain the quality of life of the patient [6,44].

(A) Topical treatment:- 1) Corticosteroids:- It is the first line treatment and considered to be the gold standard most commonly used is clobetasol propionate ointment [6]. The recommended dose is approximately 0.5 grams to be applied to the affected area daily once for a month and the alternate days for a month and then twice a week for another month for a total of three months [47].

2) Calcineurin Inhibitors:- Tacrolimus and Pimecrolimus creams act by blocking the release of inflammatory cytokines from T lymphocytes and are applied once or two times daily for a duration of 1-2 months. These are an alternative to corticosteroids though corticosteroids still remain as first line treatment [48-50].

(B) Platelet Rich Plasma:- It heals the tissue by stimulating release of cytokines and growth factors, promotes angiogenesis and cell proliferation leading to decrease of inflammation and causing damaged tissue repair and restoration of function of skin [51].

(C) UV Treatment:- 1) Phototherapy- Topical PUVA and UVA and UVB is used in treatment of LS and is indicated in case corticosteroids failure [52,53].

2) Photodynamic therapy- Photosensitising agents (5-aminolevulinic acid) at appropriate wavelengths and oxygen are used to target cells causing inflammation and fibrosis to healthy tissue. It is an option to treat when other therapies are ineffective [6].

(D) Surgical Treatment:- Surgical measures like circumcision, dilatation of meatal stenosis, urethroplasty, dilatation of introital stenosis, clitoral circumcision to improve anatomical, sexual and urinary dysfunction [54-58]. Vulvectomy to be done in cases of vulvar cancer only [6].

(E) Miscellaneous Therapy:- 1) LASER Therapy: - It is an emerging treatment therapy in which CO2 laser ablation is used causing improvement in signs and symptoms and quality of life. Fractional CO2 laser therapy has a wavelength of 10,600nm which causes ablative effect on soft tissues and has a pulsed beam protecting the tissues from overheating. It has shown good results in vaginal atrophy treatment. Laser beam is given to tissue in a fractional manner causing alternate treated and not treated areas (fractional effect) [61]. Some authors say that it should be used as an adjuvant to topical corticosteroids for effective results [59,60]. 2) HIFU (High intensity Focussed ultrasound):- It is a non-method of treatment which relieves pruritis and stimulates cell proliferation, synthesis of proteins and revascularization to repair the damaged tissue and accelerate tissue reconstruction [62].

CONCLUSION

LS is an under-diagnosed and a misdiagnosed disease with not so clear pathogenesis leading to alteration in anatomical, sexual and urinary dysfunction along with disturbance in good quality of life. New emerging treatments like energy based modalities such as fractional CO2 laser therapy and +HIFU are found to be effective and are still under study. The gold standard method to treat and prevent complications (like scarring and malignancy) is still topical corticosteroids applied for 4 to 12 weeks and tapering of dose as required. Hopefully in near future a clear pathogenetic view develops and more techniques for treatment will emerge improving the quality of life of LS patients.

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