A Review Article on Lichen Sclerosus, Affecting Ano-Genital Area in Females

Ahmed Mohammed Lutfi Al-Imam

Corresponding author

Ahmed Mohammed Lutfi Al-Imam*

*Medical doctor, Anatomist, Dermatologist, and Information Technology Specialist MD, M.Sc. (United Kingdom)

Member of European Academy of Dermatology and Venereology (EADV)

Member of National Academy of Neuropsychology (NAN)

Member of American Association of Anatomists (AAA)

Member of National Computer Science Academy (NCSA)

Department of Pathology, College of Medicine, Baghdad University, Baghdad, IRAQ
Email: tesla1452@gmail.com
Phone: +964 (0)7714 338199 (IRAQ) +44 (0)7482 571679 (UK)

Abstract

Objective: To collect detailed up-to-date knowledge, using systematic review of the medical literature specific to the dermatologic condition Lichen Sclerosus (LS), which mainly affects the ano-genital area of female patients. This article will review the epidemiology of the disease, pathogenesis, clinical features, complications, differential diagnosis, diagnostic methods, histopathology, psychosocial impact, and treatment options.

Background: LS is a chronic dermatologic condition. The condition was described at the end of the 19th century. LS incidence is higher in females than in males, affecting mainly the female ano-genital area. Diverse and crippling complications exist, including malignant transformation. Clinical features progress towards severe vulvar anatomic distortion, which results in devastating psychosocial implications. Mainstay treatments are both medical and surgical; and recent randomized controlled trials promote the use of topical calcineurin inhibitors.

Methods: A meticulous strategy was utilized across databases, led by pre-specified keywords, followed by the application of database-specific filters to scrutinize the hierarchy of available medical literature, from guidelines, systematic reviews and randomized controlled trials to medical papers with weak evidence. Certain articles were requested from the British library.

Results: Approximately 70 references were used the most relevant data were extracted. This article is divided into sections of topics, starting from an introduction to a conclusion.

Conclusion: This article will enable the medical researcher to obtain a detailed perspective of the condition LS. Thus, a researcher can seek strongest evidence for his original research.

Keywords: Lichen Sclerosus, Ano-genital, females, Extracellular Matrix Protein-1, Borrelia burgdorferi.

Methodology

A detailed search strategy was utilized across six databases: PubMed, The Cochrane Library, Scopus, metaRegister of Controlled Trials, British Association of Dermatologists (BAD) guidelines, and Open Gray. The search was conducted from June 15 to August 1, 2015.

The search was led by exhaustive and pre-specified keywords of free text, Medical Subject Headings (MeSH), and their combination. The number of keywords reached 75, and they were categorized into four main groups: Lichen Sclerosus (LS) disease nomenclature, female gender, age group, and LS therapeutics terminology. Boolean operators and truncation were used 1) to narrow and expand the search, respectively.

This was followed by the application of database-specific filters (Tables 1 and 2). 2) However, some restrictions (filters) were not applicable (N/A) due to the nature of some databases. Additionally, inclusion and 3) exclusion criteria (Table 3) were created to scrutinize the hierarchy of available medical literature, from guidelines, systematic reviews, and randomized controlled trials to medical papers with weak evidence (including anecdotal reports).

The Critical Appraisal Skills Programme (CASP) appraisal tool was used to evaluate the papers from the filtered search results. This tool was practical and convenient due to a number of reasons. Many articles failed (scored low) during the analysis via the CASP tool due to multiple factors (Table 4). Among the appraised papers that were used to create this review article, aside from textbooks (to which CASP is not applicable), three papers scored the highest:

Topical interventions for genital lichen sclerosus (Systematic review)

British Association of Dermatologists' guidelines for the management of lichen sclerosus 2010 (Guidelines)

Guidelines for the management of lichen sclerosus (Guidelines).

Table 1

Total number of papers before and after the application of filters (limits)

	PubMed	The Cochrane Library	Scopus	metaRegister of Controlled Trials	Open Grey	BAD guidelines	Total articles
Total number of papers Before Application of limits	11	3018	9	N/A	N/A	2	3040
Total number of papers after application of Limits	7	60	2	N/A	N/A	2	71

Table 2
The filters (limits) that were used for each database

Database	Applied filters
PubMed	□ English language. □ Full text articles. □ Publication date in the last 5 years, were a priority. □ Human studies only. □ Systematic reviews, guidelines, randomized controlled trial (RCT) and multicenter studies.
The Cochrane Library	□ English language. □ Publication date 2010 to 2015, were a priority. □ Human studies only. □ Full text. □ Top of the medical evidence hierarchy, were the prime target.
Scopus	□ English language. □ Articles and reviews under the topic of "Medicine" were searched. □ Literatures from all countries were included but with English as the instruction language. Keywords used were limited to "Human, child & female".
Open Gray	N/A
Meta Register of controlled trials	N/A
BAD guidelines	N/A

Table 3
Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
LS lesions affecting ano-genital and perineal region only.	Extra-genital LS lesions
Females (all age groups)	Males (all age groups)
Literature of high level of evidence	Literature of low quality level of evidence was conditionally excluded. Exclusion was based on low scoring on the CASP critical appraisal tool
Literature from the fields of dermatology, venereology, urology and enterology.	

Table 4
CASP critical appraisal tool

Advantages of CASP tool	Causes of low scoring on CASP tool
Less time consuming compared with other appraisal tools (e.g Duffy tool)	Small sample size
Appraisal is based on a series of questions up to 11 (for RCTs)	Weak randomization methods, allocation concealing and blinding techniques
Each question has a hint guiding through the evaluated paper.	High levels of bias.
Two screening questions (at the beginning of CASP)	Short duration of studies (majority were less than 3 months).
Questions covered the entire sections of the evaluated paper.	No considerable follow up period.
Questions were categorized into: validity, results and the application of results.	No data concerning the relapse rate.
Questions are answered by: "Yes", "No" and "Can't tell"	Concerning LS management, lack of defined regimen for topical therapeutic agents. Concerning LS management, lack of data on long-term safety issues of therapeutic agents (induction of vulvar cancer, activation of pre-existing human papilloma virus and alteration of serum calcium levels).

1. Introduction

(Neill, Lewis, Tatnall, & Cox, 2010; Kirtschig, Baldo, Brackenbury, Lewis, & Wojnarowska, 2011; Thomas, 2009; Goodfield, Jones, & Veale, 2010; Bunker & Neill, 2010; eMedicine, n.d.; Hallopeau, 1887; Darier, 1892; Abdelbaky, Aluru, Keegan, & Greene, 2012; Warrington & de San Lazaro, 1996)

Lichen sclerosus (LS) is chronic dermatosis with a major predilection for the ano-genital area, mainly affecting peri-menopausal and pre-pubertal females, and extragenital sites can be involved. It was known as Lichen Sclerosus et Atrophicus, but the term "et Atrophicus" was dropped in 1976 (because not all lesions have atrophy). When it affects the male external genitals, it is known as Balanitis Xerotica Obliterans (BXO). Other synonyms of LS include guttate morphoea, guttate scleroderma and white-spot disease, which mainly refer to trunk and limb involvement. Hallopeau (1887) was the first to describe LS, while Darier (1892) pioneered LS histology, and both considered LS a Lichen Planus variant. Although LS is a separate entity, others thought LS was a localized scleroderma variant.

LS in children is commonly mistaken as sexual abuse, while it causes psycho-sexual dysfunction in adults. The mainstay treatment is with super-potent topical steroids.

2. Epidemiology

(Pinelli, D'erme, & Lotti, 2013; Smith & Fischer, 2009; Wallace & Whimster, 1951; Sherman et al., 2010; Kiss, Kiraly, Kutasy, & Merksz, 2005; Simpkin & Oakley, 2007; Meyrick & Kennedy, 1986)

Female ano-genital LS is more common than BXO. There is no racial predilection; however, familial clustering exists. A high concordance rate is reported in monozygotic and dizygotic twins. The bimodal age distribution in females is peri-menopausal and pre-pubertal.

3. Pathogenesis

(Neill, Lewis, Tatnall, & Cox, 2010; Kirtschig, Baldo, Brackenbury, Lewis, & Wojnarowska, 2011; Thomas, 2009; Goodfield, Jones, & Veale, 2010; Darier, 1892; Cox, Mitchell, & Morley, 1986; Günthert, Faber, Knappe, Hellriegel, & Emons, 2008; Taylor, Guzail, & Al-azzawi, 2008; Powell & Wojnarowska, 2001; Oyama et al., 2003; Howard, Dean, Cooper, Kirtshig, & Wojnarowska, 2004; Aberer, Kollegger, Kristoferitsch, & Stanek, 1988; Ansink et al., 1994; Drut, Gómez, Drut, & Lojo, 1998; Nasca, Innocenzi, & Micali, 2006)

LS etiology is unclear, with autoimmune, hormonal, genetics, infectious and other causes incriminated; and the predilection for the ano-genital area is poorly understood (Pinelli et al., 2013). Female predominance with a bimodal age pattern and the girls' remission at puberty and menarche indicate a hormonal influence. Moreover, the oral contraceptive pills-mediated disturbance of androgen-controlled vulvar skin growth might trigger early LS, and estrogen receptor expression is critical (Cox et al., 1986; Goodfield et al., 2010; Günthert et al., 2008; Thomas, 2009).

The presence of a family history of autoimmune diseases supports the role of autoimmunity (highest at 41–60 years) (Goodfield et al., 2010; Taylor et al., 2008; Thomas, 2009). Two-thirds of LS patients had serum IgG-autoantibodies towards extracellular matrix protein-1 (*ECM-1)*. One-third of LS patients had circulating anti-*BMZ* antibodies (*BP180 and BP230*, involved in immuno-bullous dermatoses) (Goodfield et al., 2010; Oyama et al., 2003; Powell & Wojnarowska, 2001; Thomas, 2009). The geographical distribution in Germany, Austria and Japan signifies the role of *Borrelia burgdorferi* (especially in early LS). A prior history of vaginitis and chronic balanitis was also implicated. Human papilloma virus (*HPV*)

(types 6, 16, 18, 33, 45 and 51) were reported, especially in penile LS (Aberer et al., 1988; Ansink et al., 1994; Drut et al., 1998; Goodfield et al., 2010; Howard et al., 2004; Kirtschig et al., 2011).

Koebnerization occurs in LS (more with extragenital lesions) at the site of mechanical trauma. Penile LS also occurs in hypospadias, hypospadias repair and penile grafts (Darier, 1892; Goodfield et al., 2010; Kirtschig et al., 2011). Chronic ano -genital skin exposure to urine and occlusion can be a factor in urine-dribbling males and peristomal LS (mainly urostomies). LS histological changes in flexural-occluded skin tags support the role of occlusion of flacid skin (Goodfield et al., 2010; Nasc a et al., 2006; Thomas, 2009).

3.1. Immunology

(Goodfield et al., 2010; Thomas, 2009; Pinelli et al., 2013; Al-niaimi & Lyon, 2013; Regauer, Reich, & Beham-Schmid, 2002; Farrell, Dean, Millard, Charnock, & Wojnarowska, 2006; Strittmatter, Hengge, & Blecken, 2006)

Subepithelial dense lymphocytic infiltrate, with immuno-regulatory and activated *T*-cells with monoclonal gamma *T*-cells receptor (*γ-TCR)* rearrangement (Al-niaimi & Lyon, 2013).

Changes in other immunological indices also occur (Table1).

Table 1

Immunological Changes in LS

IgG/IgM/IgA, complement & fibrin are present.
IgG-autoantibodies to *ECM*-1 and Bullous pemphigoid antigens (*BPAG1*& *BPAG2*).
Skin basement membrane damage with over-expression of *laminin*, *collagen* 4 & 7.
Significant lipid peroxidation (mainly in stratum basale) confirmed *ECM-1* role.
Reduced manganese superoxide-dismutase makes cells vulnerable to oxidative stress.
Cytokine response mimics that of Lichen Planus (LP) & chronic wounds.
Increased *TNF-α, IL-1, interferon-γ, TGF-ß, CD25, CD11α* & *ICAM-1*.
Dysfunctional fibroblast & collagen over-production driven by *TGF-ß* exist.

Sources: Farrell et al., 2006; Goodfield et al., 2010; Oyama et al., 2003; Regauer et al., 2002; Sander, Ali, Dean, Thiele, & Wojanrowaska, 2004; Strittmatter et al., 2006; Thomas, 2009

3.2 Genetics

(Thomas, 2009; Goodfield et al., 2010; Taylor et al., 2008; Sander et al., 2004; Senturk et al., 2004; Scurry & Cohen, 1998; Prowse, Ktori, Chandrasekaran, Prapa, & Baithun, 2008).

Genetics is highly implicated by familial clustering, high concordance in monozygotic and dizygotic twins, autoimmune diseases-coexistence and Human Leukocyte Antigen (*HLA*) association (Table 2) (Goodfield et al., 2010; Thomas, 2009). *HLA-DQ7* has predominant LS association (Goodfield et al., 2010; Sander et al., 2004; Taylor et al., 2008; Thomas, 2009).

Table 2

HLA Association with LS.

HLA-type/subtype	Notes
HLA-DQ7, 8 or 9	Found in 78% of LS.
HLA-DRB112	Enhances the possibility of vulvar disease.
HLA-DRB10301	Confers disease protection.
HLA-DR11, DR12 & DQ7 (in men)	Associated with disease development.
HLA-B08 & B18	Lack of data, interestingly in report on 4 siblings with LS, they had an unaffected sister, which

Sources: Goodfield et al., 2010; Sander et al., 2004; Taylor et al., 2008; Thomas, 2009

High *Ki67* protein expression is found in thickened LS lesions, due to squamous cell hyperplasia or Lichen Simplex chronicus (Senturk et al., 2004). High *p16INK4A* expression with coexisting *HPV-16* in penile LS confirms *HPV*'s role in interfering with the retinoblastoma pathway (Scurry & Cohen, 1998). Genomic silencing via hyper-methylation of the *MGMT* and *RASSF2A* genes was found in vulvar squamous cell carcinoma (SCC) and LS coexisting with SCC, but was absent in isolated LS (Prowse et al., 2008).

4. Clinical Features

(Neill et al., 2010; Kirtschig et al., 2011; Thomas, 2009; Goodfield et al., 2010; Farrell et al., 2006; Guerrero et al., 2011; Pugliese, Morey, & Peterson, 2007; Ridley, 1987; Neill, Tatnall, & Cox, 2002; Hassanein, Mrstik, Hardt, Morgan, & Wilkinson, 2004; Bussen, 2009; Christman, Chen, & Holmes, 2009; Farrell, Marren, & Wojnarowska, 2000; Bonin, Gubertini, & Trevisan, 2011; Meyrick-Thomas, Ridley, McGibbon, & Black, 1988)

Spontaneous remission usually occurs in pre-pubertal girls. Peri-menopausal women are the prime LS target. Early lesions have erythema with or without hypopigmentation, then form typical porcelain-white ivory macules, papules and plaques. The genito-crural folds, inter-labial sulci, labia minora, labia majora-inner aspect, clitoris, clitoral hood and perineal body are mainly affected. In contrast to Lichen Planus (LP), mucosal involvement does not occur (sparing the cervix and vagina). LS lesions surround the anus and vulva in a figure-of-eight pattern, forming ivory atrophic papules and plaques with follicular hyperkeratosis and plugging. However, LS may resemble a macerated intertrigo with a flat and glistening appearance. LS results in scarring (Table 3), vulvar shrinkage and narrowing of the introitus (Figure 1) down to one centimeter.

Table 3

Factors Contributing to Vulvar Scarring and Shrinkage in LS

Atrophy of labia minora (labial resorption).
Atrophy of clitoris, clitoral hood with clitoral burial.
Fusion of labia minora & labia majora.
Narrowed vaginal introitus (due to anterior & posterior labial fusion).

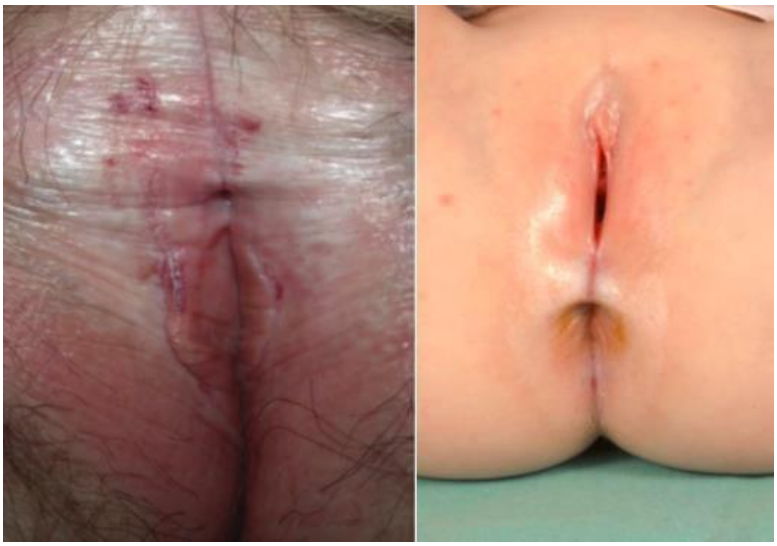

Figure 1. Gross vulvar shrinkage, right image shows typical ivory figure-of-eight pattern (Farrell et al., 2006; Goodfield et al., 2010).

The presence of purpura, ecchymosis and telangiectasia is characteristic due to skin atrophy vs. irritation, humidity and area occlusion. Edema, blistering, hemorrhagic bullae, erosions and ulcerations occur too. The main symptoms are soreness and itching (this is worse at night and disturbs sleeping), pain and dyspareunia (due to erosions, fissuring and narrowed introitus), urinary symptoms and constipation (due to irritation, and ano-genital-anatomical distortion). LS can be asymptomatic in pre-pubertal girls; such cases are commonly mistaken as sexual abuse (while sexual abuse can trigger LS via Koebnerization). Extragenital lesions with severe itching co-exist in 10% of cases, with predominant truncal distribution at pressure sites (possible Koebnerization), and scalp involvement is rare (Figure 2).

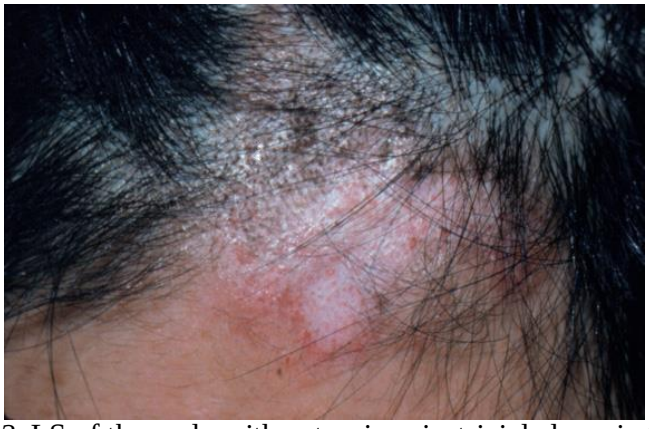

Figure 2. LS of the scalp with extensive cicatricial alopecia (Thomas, 2009).

Pre-malignant and malignant transformations occur in LS, and there is a definite link between LS and vulvar SCC, which co -exist in 5% of cases, usually arising in the vulvar-anterior part on top of the longstanding sclerotic area. Oncogenic *HPV* seems to have carcinogenic potential in pre-pubertal females. It is unknown if LS-management reduces carcinogenesis. Other superimposed pre-malignant and malignant variants include: stratum basale dysplasia, carcinoma in situ, verrucous carcinoma and basal cell carcinoma, while melanoma occurrence is rare.

Coexisting vulvar melanoma in pre-puberty is extremely rare. Hassanein et al. (2004) reported a case in a Caucasian girl in which partial vulvectomy was performed. Bussen et al. (2009) reported junctional melanocytic nevus of the labia minora in a pre-pubertal girl.

5. Complications (Farrell et al., 2006; Goodfield et al., 2010; Thomas, 2009; Ridley, 1987; Bussen, 2009):

- Malignant transformations.
- Narrowed introitus.
- Superadded infections.
- Digestive tract and urinary system problems.
- Pseudocyst of the clitoris.
- Psychosexual problems, attributed to dysesthesia, vestibulodynia and vulvodynia.

6. Diagnosis (Dx)

(Neill et al., 2010; Kirtschig et al., 2011; Thomas, 2009; Goodfield et al., 2010; Bonin, Gubertini, & Trevisan, 2011; Meyrick-Thomas, Ridley, McGibbon, & Black, 1988)

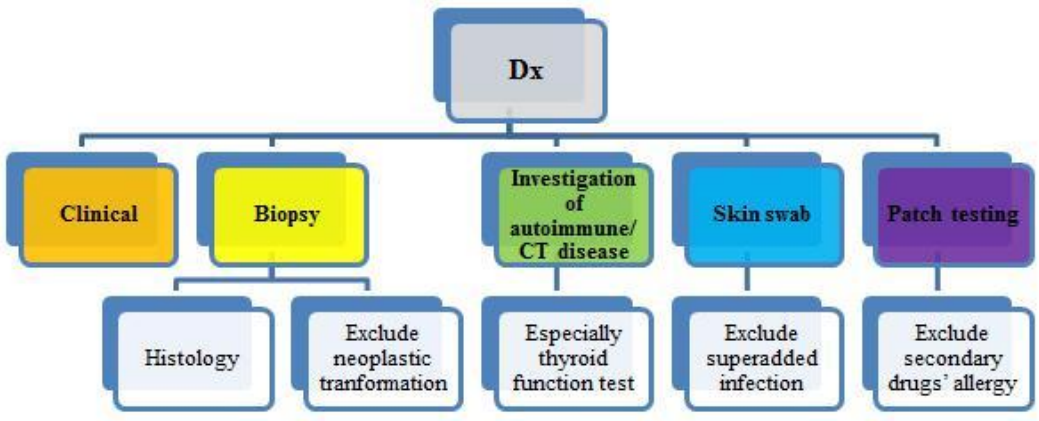

Figure 3. Diagnostic tools in LS.

7. Histopathology

(Neill et al., 2010; Thomas, 2009; Goodfield et al., 2010; Regauer & Reich, 2005; Mann & Cowan, 1973; Stanley, Vinay, & Ramzi, 2010).

Histopathology is diagnostic (except in the early stages), there is peculiar peri-vascular dense dermal mononuclear and lymphocytic infiltrate (which is initially scanty and focal) hugging the epidermis, the infiltrate becomes deeper, forming a band with the overlying thick sub-epidermal sclerotic/hyaline zone with unique changes in the dermal collagen and elastin (under EM). The sub-epidermis appears edematous, structureless and with dilated capillaries and sparse cells. Initially, there is a variable epidermal thickening, hyperkeratosis and follicular plugging. Later, there is epidermal thinning, absent rete pegs, superficial hyperkeratosis and stratum basale-vascular degeneration potentiated with dermo-epidermal clefting. Marked dermal edema (Figure 4) can precede or coexist with sclerotic changes (Goodfield et al., 2010; Kirtschig et al., 2011; Neill et al., 2010; Regauer & Reich, 2005; Stanley, Vinay, & Ramzi, 2010; Thomas, 2009).

If there are adjacent invasive carcinomas, LS frequently transitions from classic atrophy to epithelial hyperplasia and squamous cell atypia (Stanley et al., 2010).

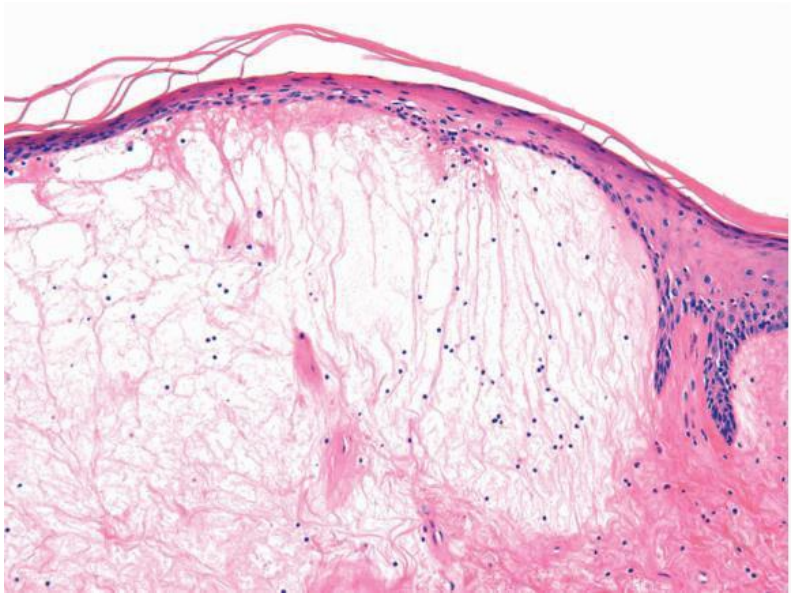

Figure 4. Evident dermal edema with lymphocytic infiltrate (Stanley et al., 2010).

8. Differential Diagnosis (DDx)

(Christman et al., 2009; Farrell et al., 2000; Neill et al., 2010; Thomas, 2009; Goodfield et al., 2010).

Vitiligo, morphoea, LP and mucous membrane pemphigoid may present with clinical similarities to LS or co-exist with LS. Clinical and histological overlap with morphoea, LP and scleroderma (Table 4) may represent the possible disease spectrum. Scalp LS may resemble "en coup de sabre" of localized Scleroderma (Christman et al., 2009; Farrell et al., 2000; Goodfield et al., 2010; Thomas, 2009).

Table 4

Medical Entities Associated with LS

Morphoea
Vitiligo
Alopecia areata (in males)
Pernicious anemia (in females)
Limited cutaneous systemic sclerosis
Systemic lupus erythematosus
Lichen planus

Source: Thomas, 2009

9. Psychosocial Impact

(Neill et al., 2010; Kirtschig et al., 2011; Warrington & de San Lazaro, 1996; Mills, 2009; AAFP, n.d.; Shasi, Chapman, Evans, & Jaleel, 2010; Brown, McKenna, Siddhi, McGrouther, & Bayat, 2008; Wikipedia, n.d.; Wehbe-alamah, Kornblau, Haderer, & Erickson, 2012; Evers et al., 2008; Hong, Koo, & Koo, 2008; Koblenzer, 2005)

A psycho-social burden occurs in LS due to chronicity, physical and genital disfigurement, sexual dysfunction, associated autoimmune disease and connective tissue diseases, and risk of neoplastic transformation. Patients have to be comforted regarding the rarity of malignancy and impossibility of infectivity to others (AAFP, n.d.; Mills, 2009).

Emotional wellbeing will be disturbed due to factors related to physical comfort and functioning, acceptability to self and others and confidence in the nature and management of the condition (Shasi et al., 2010).

LS patients can experience isolation, hopelessness, anger, low self-image, depression, anxiety, limited physical activities, work problems and sexual dysfunction. Frustration can emerge from defective knowledge of healthcare givers, resulting in a wrongful diagnosis and prolonged life disruption (Brown et al., 2008; Wikipedia, n.d.). Dalziel was the first to study LS- associated sexual dysfunction. Females reported dyspareunia, sex-avoidance and loss of sexual interest. Van et al. (2010) studied factors associated with sexual dysfunction through the Quality of Life Index (*QoL*), Dermatology Quality of Life Index (*DLQI*), Female Sexual Function Index (*FSFI*) and Female Sexual Distress Scale (*FSDS*). Patients scored low for sexual desire, arousal, lubrication, orgasm and satisfaction. Those with low *QoL* scores experienced more sexual difficulties (age-independent). Another study reported that patients worried about sexually transmitting the condition and cosmetic appearance negatively influenced libido (AAFP, n.d.; Koblenzer, 2005; Warrington & de San Lazaro, 1996).

10. Treatment

(Neill et al., 2010; Kirtschig et al., 2011; Thomas, 2009; Goodfield et al., 2010; Warrington & de San Lazaro, 1996; Kiss et al., 2005; Taylor et al., 2008; Ridley, 1987; Farrell et al., 2006; Brown et al., 2008; Van de Nieuwenhof et al., 2010; Hagedorn, Buxmeyer, Schmitt, & Bauknecht, 2002; Bousema et al., 1994; Carli, Cattaneo, Taddei, & Gianotti, 1992; Gurumurthy, Morah, Gioffre, & Cruickshank, 2012; Fischer & Rogers, 1997; Garzon & Paller, 1999; Lascano, Montes, &

Mazzini, 1964; Penneys, 1984; Shelley, Shelley, & Amurao, 2006; Prowse, Ktori, Chandrasekaran, Prapa, & Baithun, 2008; August & Milward, 1980; Hillemans et al., 1999; Kartamaa & Reitamo, 1997).

LS can be a permanent relapsing condition. Spontaneous resolution can occur at puberty and before the age of 30 in extragenital LS (Kiss et al., 2005; Taylor et al., 2008). Patients must receive written information about LS. A multi-disciplinary team approach by a dermatologist, gynecologist, urologist, psychiatrist and vulvar clinic is required (Farrell et al., 2006). Neoplastic risk must be explained, to be encouraged for periodic follow-ups (Brown et al., 2008; Kirtschig et al., 2011; Neill et al., 2010; Ridley, 1987).

10.1 Treatment in adult females

In newly diagnosed cases, super-potent topical corticosteroids, such as *Clobetasol propionate* (*Dermovate)*, are the mainstay treatment, and they are initially applied once-daily at night for 4 weeks, then every other day for the next 4 weeks and 2 times per week for the last 4 weeks (a 30 g tube is sufficient for 12 weeks). Some argue that Dermovate should be used for 6–8 weeks only (due to side effects, including steroid-induced atrophy). If there is a secondary fungal and/or bacterial infection, *Dermovate-NN* or *Dermovate* and *Nystaform* are used. Some patients achieve full remission. However, if LS symptoms recur, patients are instructed to use *Dermovate* at the previous effective frequency and when needed (30–60 g is sufficient for 1 year). Topical steroids may fail in LS (Table 5). Hagedorn et al. reported the use of intralesional steroid injection (Kirtschig et al., 2011; Neill et al., 2010; Ridley, 1987; Van de Nieuwenhof et al., 2010).

Table 5

Possible Causes of Failure of Super-Potent Topical Steroids in LS

Causes	**Notes**
Patients non-compliance	In elderly and disabled patients.
	Due to pharmaceutical company warning against use of high-
Incorrect diagnosis	
Added/coexisting problem	Medication-induced contact allergies.
	Secondary infection as candidiasis.
	Intraepithelial neoplasia.
	Malignancy.
	Psoriasis.
	Mucus membrane pemphigoid.
LS is treated, but is still symptomatic	Due to secondary sensory problem of dysaesthetic vulvodynia.
	Sexual dysfunction problems.
Mechanical problems/complications	Necessitates surgery.

Source: Van de Nieuwenhof et al., 2010

Topical testosterone has been reported effective in some cases, but they are less efficient than *Dermovate* and no more efficient than emollients. One possible explanation for the conflicting data is the alteration in the expression of androgen receptors during disease progression. Topical androgens are less commonly used due to their high cost and possible clitoral hypertrophy or virilization. Debate also exists regarding topical progesterone (Kirtschig et al., 2011; Neill et al., 2010; Ridley, 1987). Topical *calcineurin* inhibitors are promising, but there are few well-structured randomized controlled trials to use it as trustable evidence. Topical retinoids are not effective in uncomplicated cases; moreover, they are irritants and best reserved for complicated cases unresponsive to super-potent steroids.

Topical cyclosporin was reported as ineffective in one study. Regarding systemic therapeutics, Bousema et al. (1994) reported the effective use of Acitretin (oral retinoid) at 20–30 mg/day in severe vulvar LS. Administered by a specialist, retinoids are to be used with caution during childbearing age due to their teratogenic potential. Hydroxychloroquine can be useful at 125–150 mg/day up to a few months, but ocular S/E is dangerous (Bousema et al., 1994; Hagedorn et al., 2002; Kirtschig et al., 2011; Neill et al., 2010; Ridley, 1987). Surgical intervention (vulvectomy and Fenton's median perineotomy) are reserved for complicated LS cases. However, LS with dysplastic foci are conservatively treated with regular follow-up. Even with radical surgery, 80% of LS recurs around the surgical site (Carli et al., 1992; Goodfield et al., 2010; Ridley, 1987; Thomas,

10.2 Treatment of sexual problems

Collaboration with a psychiatrist and sexologist is needed. In selected cases, emollients or estrogen creams are used before and after intercourse. This safe and cheap method will reduce the topical steroid-dosage requirement. Dysesthesia will not respond to topical steroids, and if there is no response to 5% lignocaine ointment, gabapentin and amitriptyline use is justified. Surgical correction of the distorted vulva may help (Ridley, 1987; Warrington & de San Lazaro, 1996).

10.3 Treatment in pre-pubertal girls

Betamethasone dipropionate is successful in vulvar LS without the need for maintenance therapy, and subsequent studies have reported the effectiveness of *Dermovate* at a twice-daily application for 6–8 weeks. Topical estrogen was beneficial in one study (Fischer & Rogers, 1997; Garzon & Paller, 1999; Gurumurthy et al., 2012; Ridley, 1987).

10.4 New and unlicensed treatment

Topical *calcineurin* inhibitors (pimecrolimus and tacrolimus) are promising but unlicensed as steroid- sparing alternatives, and are best used in unresponsive cases to potent topical steroids. However, the long-term safety of these immunosuppressants (neoplastic transformation induction and *HPV* activation) is unknown, and they are better used in short courses. For response achieved within 16–24 weeks, one protocol showed the efficacy of 0.1% tacrolimus at a twice-daily application for 16 weeks. Contra-indications are pregnancy and breastfeeding (Goodfield et al., 2010; Kirtschig et al., 2011; Neill et al., 2010; Ridley, 1987; Thomas, 2009).

Penneys et al. reported good LS improvement at various sites after using *potassium para-aminobenzoate* at 4–24 g/day, and others reported the benefits of anabolic steroids, anti- histamines and anti-pruritics (Ridley, 1987; Shelley et al., 2006). The role of *Borrelia* has yet to be confirmed; however, Shelley et al. (2006) recommend intramuscular ceftriaxone every 3 weeks or intramuscular penicillin every 2–3 weeks in addition to oral penicillin or cephalosporin. Similarly, the use of prophylactic *HPV*

vaccine may play a role (August & Milward, 1980; Prowse et al., 2008). Cryotherapy can be effective in vulvar LS that is unresponsive to topical steroids. CO_2 laser, photodynamic therapy and phototherapy were reported to be effective. High- intensity focused ultrasound (HIFU) may be safe and effective (August & Milward, 1980; Goodfield et al., 2010; Hillemans et al., 1999; Kartamaa & Reitamo, 1997; Prowse et al., 2008; Ridley, 1987; Ruan et al., 2010; Thomas, 2009).

11. Follow-up

(Goodfield et al., 2010; Kirtschig et al., 2011; Neill et al., 2010; Ridley, 1987; Thomas, 2009) Patients follow-up is essential, and long-term follow-up in a specialized clinic is reserved for complicated LS (Table 6).

Table 6

General Guidelines for LS follow-up

After 2–3 months for assessing the response to treatment, if the patient's response is good, another assessment is scheduled after 6 months.
Active disease to be assessed when needed.
Annual review for stable cases is recommended.
If patient reports a suspicious change or a lump, an urgent medical consultation is to be made.

Source: Goodfield et al., 2010; Ridley, 1987; Thomas, 2009

Conclusion

LS is a chronic relapsing skin disease with very high female predisposition and tropism to the ano-genital area. Its pathogenesis is still unclear. Malignant transformation can occur, but is rare. Its histology is diagnostic. Patients can experience psychosocial and sexual dysfunctions. The main stay treatment is with potent topical steroids. However, topical calcineurin inhibitors are promising alternatives.

References

AAFP. (n.d.). http://www.aafp.org/afp/2008/0201/p321.html

Abdelbaky, A. M., Aluru, P., Keegan, P., & Greene, D. R. (2012). Development of male genital lichen sclerosus in penile reconstruction skin grafts after cancer surgery: An unreported complication. *BJU Int, 109*(5), 776–9.

Aberer, E., Kollegger, H., Kristoferitsch, W., & Stanek, G. (1988). Neuroborreliosis in morphea and lichen sclerosus et atrophicus. *J Am Acad Dermatol, 19*, 820–5.

Al-niaimi, F., & Lyon, C. (2013). Peristomal lichen sclerosus: The role of occlusion and urine exposure? *Br J Dermatol, 168*(3), 643–6.

Ansink, A. C., Krul, M. R. L., de Weger, R. A., Kleyne, J. A., Pijpers, H., Van Tinteren H., Heintz, A. P. (1994). Human papillomavirus, lichen sclerosus, and squamous cell carcinoma of the vulva: Detection and prognostic significance. *Gynecol Oncol, 52*, 180– 4.

August, P. J., & Milward, T. M. (1980). Cryosurgery in the treatment of lichen sclerosus et atrophicus of the vulva. *Br J Dermatol, 103*, 667–70.

Bonin, S., Gubertini, N., & Trevisan, G. (2011). Lichen sclerosus et atrophicans,

scleroderma en coup de sabre and Lyme borreliosis. *Dermatol Rep*, *3*(2).

Bousema, M. T., Romppanen, U., Geiger, J. M., Baudin, M., Vähä-Eskeli, K., Vartiainen, J., & Vuopala, S. (1994). Acitretin in the treatment of severe lichen sclerosus et atrophicus of the vulva: A double-blind, placebo-controlled study. *J Am Acad Dermatol*, *30*, 225–31.

Brown, B. C., McKenna, S. P., Siddhi, K., McGrouther, D. A., & Bayat. A. (2008). The hidden cost of skin scars: Quality of life after skin scarring, *J Plast Reconstr Aesthet Surg*, *61*(9), 1049–58.

Bunker, C. B., & Neill, S. M. (2010). The genital, perianal and umbilical regions. In T. B., S. B., N. C., C. G. (Eds.), *Rook's textbook of dermatology* (8th ed.) (pp. 3705–3806). Oxford, UK: Wiley-Blackwell.

Bussen, S. S. (2009). Melanocytic proliferations associated with lichen sclerosus in adolescence. *Arch Gynecol Obstet, 280*(6), 1039–40.

Carli, P., Cattaneo, A., Taddei, G., & Gianotti, B. (1992). Topical cyclosporine in the treatment of vulvar lichen sclerosus: Clinical, histologic and immunohistochemical findings. *Arch Dermatol, 128,* 1548–9.

Christman, M. S., Chen, J. T., & Holmes, N. M. (2009). Obstructive complications of lichen sclerosus. *J Pediatr Urol, 5*(3), 165–9.

Cox, N. H., Mitchell, J. N. S., & Morley, W. N. (1986). Lichen sclerosus et atrophicus in non-identical female twins. *Br J Dermatol, 115*, 743–6.

Darier, J. (1892). Lichen sclerosus. *Ann Dermatol Syphiligr, 3*, 833.

Drut, R. M., Gómez, M. A., Drut, R., & Lojo, M. M. (1998). Human papillomavirus is present in some cases of childhood penile lichen sclerosus: An in situ hybridization and SP-PCR study. *Pediatr Dermatol, 15*, 85–90. eMedicine (n.d.). http://emedicine.com

Evers, A. W., Duller, P., Van de kerkhof, P. C., van der Valk, P. G., de Jong, E.M., Gerritsen, M. J., … Kraaimaat, F. W. (2008). The Impact of Chronic Skin Disease on Daily Life (ISDL): A generic and dermatology-specific health instrument. *Br J Dermatol*, *158*(1), 101–8.

Farrell, A. M., Dean, D., Millard, P. R., Charnock, F. M., & Wojnarowska, F. (2006). Cytokine alterations in lichen sclerosus: An immunohistochemical study. *Br J Dermatol*, *155*, 931– 40.

Farrell, A. M., Marren, P. M., & Wojnarowska, F. (2000). Genital lichen sclerosus associated with morphoea or systemic sclerosis: Clinical and HLA characteristics. *Br J Dermatol*, *143*, 598–603.

Fischer, G., & Rogers, M. (1997). Treatment of childhood vulvar lichen sclerosus with potent topical corticosteroid. *Pediatr Dermatol*, *14*, 235–8.

Garzon, M. C., & Paller, A. S. (1999). Ultrapotent topical corticosteroid treatment of childhood lichen sclerosus. *Arch Dermatol*, *135*, 525–8.

Goodfield, M. J. D., Jones, S. K., & Veale, D. J. (2010). The 'connective tissue diseases'. In T. B., S. B., N. C., C. G. (Eds.), *Rook's textbook of dermatology* (8th ed.) (pp. 2475–612). Oxford, UK: Wiley-Blackwell.

Guerrero, D., Guarch, R., Ojer, A., Casas, J. M., Méndez-Meca, C., Esteller, M., Puras, A. (2011). Differential hypermethylation of genes in vulvar cancer and lichen sclerosus coexisting or not with vulvar cancer. *Int J Cancer*, *128*(12), 2853–64.

Günthert, A. R., Faber, M., Knappe, G., Hellriegel, S., & Emons, G. (2008). Early onset vulvar lichen sclerosus in premenopausal women and oral contraceptives. *Eur J Obstet Gynecol Reprod Biol, 137*(1), 56–60.

Gurumurthy, M., Morah, N., Gioffre, G., & Cruickshank, M. E. (2012). The surgical management of complications of vulvar lichen sclerosus. *Eur J Obstet Gynecol Reprod Biol, 162*(1), 79–82.

Hagedorn, M., Buxmeyer, B., Schmitt, Y., & Bauknecht, T. (2002). Survey of genital lichen sclerosus in women and men. *Arch Gynecol Obstet, 266*(2), 86–91.

Hallopeau, H. (1887). Lichen plan, atrophique. *Ann Dermatol Syphiligr, 8,* 790–4. Hassanein, A. M., Mrstik, M. E., Hardt, N. S., Morgan, L. A., & Wilkinson, E. J. (2004).

Malignant melanoma associated with lichen sclerosus in the vulva of a 10-year-old. *Pediatr Dermatol, 21*(4), 473–6.

Hillemans, P., Untch, M., Prove, F., Baumgartner, R., Hillemanns, M., & Korell, M. (1999). Photodynamic therapy of vulvar lichen sclerosus with 5-aminolevulinic acid. *Obstet Gynecol, 93,* 71–4.

Hong, J., Koo, B., & Koo, J. (2008). The psychosocial and occupational impact of chronic skin disease. *Dermatol Ther, 21*(1), 54– 9.

Howard, A., Dean, D., Cooper, S., Kirtshig, G., & Wojnarowska, F. (2004). Circulating basement membrane zone antibodies are found in lichen sclerosus of the vulva. *Australas J Dermatol, 45,* 12–15.

Kartamaa, M., & Reitamo, S. (1997). Treatment of lichen sclerosus with carbon dioxide laser vaporization. *Br J Dermatol, 136,* 356–9.

Kirtschig, C. C., Baldo, G., Brackenbury, M., Lewis, F., & Wojnarowska, F. (2011). Topical interventions for genital lichen sclerosus. *Cochrane Database Syst Rev,* (12):CD008240.Chi.

Kiss, A., Kiraly, L., Kutasy, B., & Merksz, M. (2005). High incidence of balanitis xerotica obliterans in boys with phimosis: Prospective 10-year study. *Pediatr Dermatol, 22*, 305– 8.

Koblenzer, C. S. (2005). The emotional impact of chronic and disabling skin disease: A psychoanalytic perspective. *Dermatol Clin, 23*(4), 619–27.

Lascano, E. F., Montes, L. F., & Mazzini, M. A. (1964). Tissue changes in lichen sclerosus in children following local application of oestrogens. *Br J Dermatol, 76,* 496–7.

Mann, P. R., & Cowan, M. A. (1973). Ultrastructural changes in four cases of lichen sclerosus et atrophicus. *Br J Dermatol, 89,* 223–31.

Meyrick Thomas, R. H., & Kennedy, C. T. C. (1986). The development of lichen sclerosus et atrophicus in monozygotic twin girls. *Br J Dermatol, 114*, 377–9.

Meyrick-Thomas, R. H., Ridley, C. M., McGibbon, D. H., & Black, M. M. (1988). Lichen sclerosus and autoimmunity – A study of 350 women. *Br J Dermatol, 118*, 41–46.

Mills, S. E. 2009. *Sternberg's diagnostic surgical pathology*. USA: LWW.

Nasca, M. R., Innocenzi, D., & Micali, G. (2006). Association of penile lichen sclerosus and oncogenic human papilloma virus infection. *Int J Dermatol, 45*, 681–3.

Neill, S., Tatnall, F., & Cox, N. (2002). Guidelines for the management of lichen sclerosus. *Br J Dermatol, 147*(4), 640–649.

Neill, S. M., Lewis, F. M., Tatnall, F. M., & Cox, N. H. (2010). British Association of Dermatologists' guidelines for the management of lichen sclerosus 2010. *Br J Dermatol, 163*(4), 672–82.

Oyama, N., Chan, I., Neill, S. M., Hamada, T., South, A. P., Wessagowit, V., … McGrath, J. A. (2003). Autoantibodies to extracellular matrix protein 1 in lichen sclerosus. *Lancet, 362*, 118–23.

Penneys, N. S. (1984). Treatment of lichen sclerosus with potassium paraaminobenzoate. *J Am Acad Dermatol, 10*, 1039–42.

Pinelli, S., D'erme, A. M., & Lotti, T. (2013). Management of sexual dysfunction due to vulvar lichen sclerosus in postmenopausal women. *Dermatol Ther, 26*(1), 79–82.

Powell, J., & Wojnarowska, F. (2001). Childhood vulvar sclerosus: An increasingly common problem. *J Am Acad Dermatol, 44*, 803–6.

Prowse, D. M., Ktori, E. N., Chandrasekaran, D., Prapa, A., & Baithun, S. (2008). Human papillomavirus-associated increase in p16INK4A expression in penile lichen sclerosus and squamous cell carcinoma. *Br J Dermatol, 158*(2), 261–5.

Pugliese, J. M., Morey, A. F., & Peterson, A. C. (2007). Lichen sclerosus: Review of the literature and current recommendations for management. *J Urol, 178*, 2268–76.

Regauer, S., Reich, O., & Beham-Schmid, C. (2002). Monoclonal gamma-T-cell receptor rearrangement in vulvar lichen sclerosus and squamous cell carcinomas. *Am J Pathol, 160*,1035–1045.

Regauer, S., & Reich, O. (2005). Early vulvar lichen sclerosus: A histological challenge. *Histopathology, 47*, 340–7.

Ridley, C. M. (1987). Lichen sclerosus et atrophicus. *Arch Dermatol, 23,* 457–60.

Ruan, L., Xie, Z., Wang, H., Jiang, J., Shi, H., & Xu, J. (2010). High-intensity focused ultrasound treatment for non-neoplastic epithelial disorders of the vulva. *Int J Gynaecol Obstet, 109*(2), 167–70.

Sander, C. S., Ali, I., Dean, D., Thiele, J. J., & Wojanrowaska, F. (2004). Oxidative stress is implicated in the pathogenesis of lichen sclerosus. *Br J Dermatol, 151*, 627–35.

Scurry, B., & Cohen, A. (1998). Ki67 expression in lichen sclerosus of vulva in patients with and without associated squamous cell carcinoma. *Histopathology, 32*(5), 399–404.

Senturk, N., Aydin, F., Birinci, A., Yildiz, L., Canturk, T., Durupinar, B., & Turanli, A. (2004).

Coexistence of HLA B08 and HLA B18 in four siblings with lichen sclerosus. *Dermatology, 208,* 64–6.

Shasi, P. B., Chapman, H. T., Evans, D. T., & Jaleel, H. (2010). Psychological and psychiatric morbidity in lichen sclerosus in a cohort recruited from a genitourinary medicine clinic. *Int J STD AIDS, 21*(1), 17–8.

Shelley, W. B., Shelley, E. D., & Amurao, C. V. (2006). Treatment of lichen sclerosus with antibiotics. *Int J Dermatol, 45*(9), 1104–6.

Sherman, V., McPherson, T., Baldo, M., Salim, A., Gao, X. H., & Wojnarowska, F. (2010). The high rate of familial lichen sclerosus suggests a genetic contribution: An observational cohort study. *J Eur Acad Dermatol Venereol.*

Simpkin, S., & Oakley, A. (2007). Clinical review of 202 patients with vulval lichen sclerosus: A possible association with psoriasis. *Australas J Dermatol, 48*, 28–31.

Smith, S. D., & Fischer, G. (2009). Paediatric vulval lichen sclerosus. *Australas J Dermatol, 50*(4), 243–8. Stanley L., Vinay, K., & Ramzi, S. (2010).

Robbins and Cotran pathologic basis of disease (8th ed.). Philadelphia, PA: Saunders/Elsevier.

Strittmatter, H. J., Hengge, U. R., & Blecken, S. R. (2006). Calcineurin antagonists in vulvar lichen sclerosus. *Arch Gynecol Obstet, 274*(5), 266–70.

Taylor, A. H., Guzail, M., & Al-azzawi, F. (2008). Differential expression of oestrogen receptor isoforms and androgen receptor in the normal vulva and vagina compared with vulval lichen sclerosus and chronic vaginitis. *Br J Dermatol, 158*(2), 319–28.

Thomas, B. (2009). Disorders of the genitalia, perineum, and anus. In W. Klaus & A. Richard (Eds.), *Fitzpatrick's color atlas and synopsis of clinical dermatology* (6th ed.) (pp. 1046– 66). USA: McGraw-Hill Professional.

Van de nieuwenhof, H. P., Meeuwis, K. A., Nieboer, T. E., Vergeer, M. C., Massuger, L. F., & De hullu, J. A. (2010). The effect of vulvar lichen sclerosus on quality of life and sexual functioning. *J Psychosom Obstet Gynaecol, 31*(4), 279–84.

Wallace, H. J., & Whimster, I. (1951). Vulval atrophy and leukoplakia. *Br J Dermatol, 63*, 241– 57.

Warrington, S. A., & de San Lazaro, C. (1996). Lichen sclerosus et atrophicus and sexual abuse. *Arch Dis Child, 75,* 512–6.

Wehbe-alamah, H., Kornblau, B. L., Haderer, J., & Erickson, J. (2012). Silent no more! The lived experiences of women with lichen sclerosis. *J Am Acad Nurse Pract, 24*(8), 499–505.

Wikipedia, the Free Encyclopedia. (n.d.).

Lichen sclerosus. Retrieved from http://en.wikipedia.org/wiki/Lichen_sclerosus#Psychology.