Reconstructive Urology

Pathophysiology, Clinical Manifestations, and Treatment of Lichen Sclerosus: A Systematic Review

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OBJECTIVE To elucidate current understanding on the pathophysiological mechanism of genital lichen sclerosus (LS), urologic manifestations, and treatment options.

MATERIALS AND METHODS The Medline/PubMed and Embase databases were systematically reviewed for publications pertaining to LS. After applying inclusion and exclusion criteria, references were assessed for relevance to the pathophysiology, presentation, and treatment of LS by title and abstract review by 2 independent reviewers, yielding 186 articles for assessment.

RESULTS The contemporary understanding of the epidemiology and histology of LS is reviewed herein. Additionally, we explore in detail the 3 hypotheses regarding the pathophysiological mechanism contributing to disease presentation: infectious etiology, primary immune dysregulation, and the isotraumatopic response. We summarize the available biological evidence supporting each hypothesis. This discussion provides context for understanding LS morbidity and may spur new avenues of research. For the clinician, we review the clinical presentation of disease, including the risk of progression to squamous cell carcinoma. The current medical and surgical treatment options are also detailed.

CONCLUSION LS remains a potentially insidious disease which may lead to debilitating urinary and sexual dysfunction. Cross disciplinary research should aim for earlier detection, as well as more effective and durable treatment. The exact cause of LS remains unknown. UROLOGY 00: 1–9, 2019.

Lichen sclerosus (LS) is a chronic inflammatory and scarring disease of the skin of unknown etiology. The most common site of involvement is the anogenital region. Male patients often present with white penile lesions or plaques, pruritis, painful erections and voiding, and bleeding or ulceration with intercourse.[1] In severe cases, the foreskin thickens and can become phimotic, with development of urethral strictures. In women, the most common anogenital symptoms include pain, vulvar pruritis, dysuria, and dyspareunia.[2] Although histologic descriptions and clinical diagnoses of LS date back to the mid-20th century, the pathophysiological mechanism remains largely elusive. A formal review of LS presentation and management was last outlined over a decade ago.[3] Over the past 10 years, laboratory research has sought to characterize aberrations in the dermal-epidermal junction of LS tissue samples, in addition to identifying candidate molecular targets of the immune system.[4-12]

EPIDEMIOLOGY

The exact prevalence of LS is unknown and generally considered underreported because of provider lack of familiarity and asymptomatic presentations or discomfiture.[13] Early estimations based on referrals to dermatology practices suggest the prevalence is between 1:300 and 1:1000.[14] The disease affects both women and men, though the ratio of women to men based on current estimates is approximately 3:1 to 10:1.[15] A report from a general gynecology practice estimated the prevalence to be 1.7% among females.[16] Though LS can occur at any age, the age of symptom onset is classically bimodal: in females, incidence of LS peaks in prepubertal and

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postmenopausal ages.[2,17,18] In males, LS has also been referred to as Balanitis Xerotica Obliterans (BXO). Two large sample cross-sectional studies of male LS patients estimate the prevalence to be between 0.0014% and 0.07%.[19,20] In males, onset peaks at a young age and then again in adulthood.[2,17,18]

Clinical Features

LS can have a benign or insidious course that may be associated with significant urologic and sexual morbidities if untreated. The most common early clinical features on examination in men and women include white plaques, atrophic skin, erythema, erosions, and varying amounts of sclerosus in the anogenital region.[1,2] Perianal involvement is not common in men.[21] As the disease progresses, men present with complaints of increasing phimosis and pain associated with erections as LS usually affects the glans and foreskin.[1]

Diagnosis and Treatment

In many cases, a clinical diagnosis is made if patients present with signs and symptoms of LS. A confirmatory biopsy with histologic inspection may be indicated if the case is complex or atypical, if there is pigmentation or suspicion of neoplastic change, if the patient does not respond to treatment, or if there is clinical doubt.[2] The differential diagnosis includes mucosal or erosive lichen planus, graft vs host disease, inverse psoriasis, eczema, vitiligo, morphea, plasma cell vulvitis/balanitis, vulval/penile intraepithelial neoplasia, and squamous cell carcinomas (SCCs).[15]

First-line management for LS in both men and women is topical corticosteroids. Specifically, clobetasol propionate 0.05% (ointment or cream) 1-2 times daily for 1 month, with reduced application frequency for an additional 2 months, is beneficial.[2,15] Depending on study design, overall response rates to clobetasol propionate 0.05% range from 73% to 90%.[22-24] This treatment is safe and efficacious, and has a low likelihood of severe side effects.[2,15] Early and aggressive treatment has been shown to be beneficial in halting progression and may even cause regression.[25] Thus, treatment is recommended for asymptomatic patients with clinically active LS.[13] Some clinicians advocate for long-term topical corticosteroids. Off-label use of calcineurin inhibitors such as tacrolimus 0.1% (response rate: 63%)[26] and pimecrolimus (response rate: 53%)[27] have been shown to be a lesser but still effective treatment alternative to corticosteroids, but should be considered experimental as it is unknown if they are carcinogenic.[15,28,29]

In male patients with altered structural anatomy due to scarring, circumcision (long-term cure rate: 92%)[30] and/or meatotomy (success rate: 87%)[31] are indicated. In more severe cases in which patients present with stricture, urethroplasty or perineal urethrostomy is recommended. Urethroplasty often involves the use of nongenital skin grafts (eg, buccal mucosa).[32] Case series evaluating buccal mucosa graft urethroplasty has shown success rates between 88% and 91% success rate over 32.5-month follow-up.[33,34] Two-stage urethroplasty procedures may be necessary in severe cases. Surgical excision of vulvar tissue is not recommended in women with refractory disease. However, cryotherapy is useful in relieving severe itch in women. Seventy-five percent of patients in a series of 12 indicated symptom relief on cryotherapy. Photodynamic therapy (10/12 patients reported some improvement),[35] UVA1 therapy (5/7 patients reported some improvement),[36] and laser treatments (9/10 patients reported some improvement)[37] have been used with some success in women but are not the recommended approaches.[13] Other therapies with mixed evidence of effect include cyclosporine, methotrexate, and retinoids.[13] Hormonal treatments are no longer recommended; however, if atrophy is present in postmenopausal women in addition to LS, then local estrogen treatment is recommended.

Given this clinical context, the focus of this systematic review is to describe current knowledge of the pathophysiology of LS.[3] After a brief overview of the clinical and histologic characteristics of LS, we highlight proposed pathophysiological mechanisms contributing to LS etiology. We also outline 3 unifying hypotheses regarding the pathophysiology of LS: first, the theory that infections trigger and sustain an immune response; second, that primary immune dysregulation—or possibly autoimmunity—are permissive or causal of the chronic inflammatory condition; and third, that occluded exposure to liquid irritants such as urine results in cutaneous trauma that triggers the disease. Finally, we discuss directions for future research.

METHODS

The following search query was entered into Medline/PubMed and Embase: ["physiopathology" OR "etiology" OR "pathophysiology" OR "pathogenesis" OR "etiology" OR "physiopathology" OR "aetiology" OR "gene"] AND ["lichen sclerosus et atrophicus" OR "vulvar lichen sclerosus" OR "balanitis xerotica obliterans"]. This query yielded 1143 articles. We excluded non-English articles and nonhuman studies. We included only original research and articles published in 1970 or later. Two independent reviewers (AL, KF) applied initial exclusion and inclusion criteria with 96.5% agreement. Differences were adjudicated via consensus, and 360 articles remained. Two independent reviewers (AL, KF) then assessed relevance of each article to the pathophysiology and etiology of LS by title and abstract review resulting in the final 186 articles for this review (Supplemental Fig. 1). The protocol for this review has been reviewed and approved by the PROSPERO network (registration number: CRD42019139432).

RESULTS

LS in Men

Meatal stenosis and urethral stricture are also seen in men with LS and can result in significant morbidity for those affected with recurrence rates between 20% and 50%.[38,39] If untreated, an inflexible phimotic foreskin may constrict the glans, which can manifest as a scrotalized appearance of penile shaft skin.

Involvement of the meatus (Supplemental Fig. 2) and urethra in men can lead to urinary morbidity including changes in urinary stream and dysuria, or in severe cases urinary retention and subsequent renal failure.[1,2] In these cases, LS can progress proximally from the glans skin to involve the fossa navicularis and at times a significant portion of the urethra causing pan-urethral stricture (Supplemental Fig. 3).[2] Even in the absence of distal to proximal urethral disease progression, LS has been found to be associated with isolated bulbar urethral strictures.[40] LS may account for as much as 10% of urethral stricture disease among men.[38] Another association of LS in men is to concealed-buried penis, though at present, current research does not suggest a directionality in this relationship.[41]

LS in Women

Complaint of vulvar pruritus is a typical presentation in women, which can worsen at night and affect sleep.[2] A characteristic figure of 8 pattern of skin changes is often seen around the vulva and anus in patches or plaques with fragile, thinned, and atrophic skin.[1] Dyspareunia can occur as a result of a narrowed vaginal introitus, as well as the presence of erosions and fissures in the atrophic skin.[2] Voiding complaints can occur but are much less common in women than in men. In severe, rare cases, women present with meatal stenosis (Supplemental Fig. 4).[42]

Malignant Transformation

Though estimates vary, the risk of progression to SCC is approximately 3%-6% in females, and 2%-8% in males.[30,43-46] Retrospective cohort studies of female SCC patients revealed 61%-65% had LS in the background of SCC.[47,48] Though uncommon, case reports exist of LS patients developing verrucous carcinoma, basal cell carcinoma, and malignant melanoma.[49-51]

Histology and Electron Microscopy

LS has a characteristic histologic appearance that includes lichenoid interphase dermatitis, epidermal atrophy, and hyperkeratosis, with or without vacuolar degeneration of the basal cell layer of the epidermis. These classic histologic features are shown in Supplemental Figs. 5 and 6. Typical findings on electron microscopy (EM) and histology are summarized in Table 1; dermopathologic review of suspected cases is highly recommended.

ETIOLOGY

Clinical Risk Factors

LS may be associated with environmental factors and nonautoimmune comorbidities. The most commonly cited risk in men is lack of circumcision.[52,53] Mallon et al noted an age-adjusted odds ratio of 53.55 (95% confidence interval [CI]: 7.24-395.88) in association to uncircumcised male patients.[53] Injury to genital skin can increase the risk of LS as can friction, genital piercings for jewelry, and surgery.[54,55] An investigation into LS and medical comorbidities demonstrated an association between LS and higher mean body mass index (BMI) (31.0 vs 28.1, $P = .001$), diabetes mellitus (odds ratio [OR] = 2.04, $P = .03$), and a weaker association with coronary artery disease (OR = 1.88, $P = .05$).[56] This finding is corroborated by additional studies, which have demonstrated an association between LS and BMI (OR = 1.089, 95% CI: 1.050-1.130), diabetes mellitus (OR = 2.71, 95% CI: 1.79-4.11), tobacco usage (OR = 2.0, 95% CI: 1.36-3.40), hyperlipidemia (OR = 3.1, 95% CI: 1.1-8.2), and hypertension (OR = 2.028, 95% CI: 1.21-3.41).[38,55,57] Evidence from case reports suggests certain exposures—such as sunburns or radiation treatment—may increase the risk of LS.[58,59] Little evidence of drug-induced LS exists, though Baldo et al found in their comparison of 200 women with vulval LS to 974 controls that LS patients were less likely to be on ACE inhibitors (3% vs 12%, $P = .001$) or beta-blockers (4% vs 10%, $P < .01$).[60] Patients with postmicturition microincontinence may have increased risk, particularly in the uncircumcised male as indicated by several case series.[61-63]

Genetic Risk Factors

A variety of studies investigated the genetic basis of LS. The fact that female LS can run in families is well established.[64-67] Salim et al interviewed 400 individuals with LS and found that 15% had a family history of the disease.[64] By contrast, genetics may play a considerably smaller role in male genital LS.[68-70] Investigators have predominantly evaluated human leukocyte antigen (HLA) genotypes, which are hypothesized to play a role in the pathogenesis of LS. The most common association is with HLA-DQ7.[68,71,72] A summary of previous research findings on the association between HLA genotype and LS can be found in Table 2. This large body of research identifies numerous possible genetic susceptibilities to LS disease, but does not indicate a specific immunogenetic profile that universally confers susceptibility to disease.

Table 1. Key features of LS on histology and electron microscopy (EM)

Common Histologic Findings[89-93]	Electron Microscopy Findings[89-91,94]
Lichenoid interphase dermatitis	Holes in basal lamina
Epidermal atrophy	Collagen fibrils in intracellular spaces
Hyperkeratosis	Absent capillary loop networks
Pale-staining, pauci-cellular zone within the upper dermis	Dilated blood vessels, lymphocyte infiltrate or vasculitis
Deep band-like infiltrate of mononuclear inflammatory cells.	Perineural inflammation
	Disorganized collagen in dermis
	Mast cells / eosinophils variable
Less Common Histologic findings[89,90,95-97]	
Hypertrophic epidermis	
Subepidermal clefting	
Thickening of the basement membrane with collagen IV and VII	

Table 2. Literature reporting human leukocyte antigen associations in lichen sclerosus patients

Authors	Year	#Patients	Correction	Increased in LS	Decreased in LS
Harrington & Gelsthorpe[98]	1981	50	Bonferroni	-B40	-
Holt & Darke[99]	1983	26	Yates	-Aw31* -B40	-
Meyrick Thomas et al[100]	1984	120	Yates	No association in class I antigens	-
Friedrich & MacLaren[66]	1984	6	N/A	-B44 -DRW6	-
Sideri et al[101]	1988	68	Bonferroni	-B21* -DR5 -DR7	-
Purcell et al[69]	1990	35	N/C	-A29* -B44* -B8 -DR3	-
Marren et al[71]	1995	84	Yates & Bonferroni	-DQ7* -DQ8 -DQ9	-DQ2 -DQ5 -DQ6
Azurdia et al[68]	1999	58	Yates	-DQ7* -DR11* -DR12*	-DQ6*
Powell et al[72]	2000	30	Yates	-DQ7*	-DR17*
Senturk et al[70]	2004	4	N/A	-B*08 [a] -B*18	-
Gao et al[102]	2005	187	Bonferroni	-DRB1*12* - DRB1*12/DQB1*0301/04/09/010*	-DRB1*0301/04* - DRB1*03/DQB1*02DRB1*0301/DQB1*0201/02/03*
Aslanian et al[103]	2006	8	N/A	-B*15 -B*57 -CW*03 -CW*07 -CW*18 -DRB1*04 -DRB1*07 -DRB4*	-
Liu et al[104]	2015	76	N/C	-A*11* -B*13* -B*15* -DRB1*12*	-A*31* -DRB1*01* -DRB1*03*
Farrell et al[105]	2000	9	N/A	-DQ7	

N/A, not applicable; N/C, not corrected.
* Statistically significant finding after correction.

Hypothesized Pathophysiology

There are 3 competing theories as to the possible cause of LS: infectious, autoimmune, and chronic irritation. The primary infectious processes previously investigated include Borrelia burgdorferi (B. burgdorferi), Epstein Barr Virus (EBV), Hepatitis C Virus (HCV), and Human Papilloma Virus (HPV), as summarized in Table 3. In summary, these infections have been found to be associated with LS in about 0%-75% of cases. At present, there is insufficient evidence to conclude infections are a causative agent in the development of LS.

The autoimmunity hypothesis suggests that a localized loss of immune self-tolerance allows for humoral or cell-mediated response to LS-specific antigens. The best estimates of any autoimmune disorder co-occurring with LS are among women range from 18.9% to 28.4%.[73,74] Autoimmune thyroid disease or the presence of thyroid autoantibodies ranges from 0% to 39% among women with LS, with the largest study (n = 396) reporting 15.2%.[57,74,75] Cooper et al investigated 190 women with LS and reported 10.5% had vitiligo and 2.6% had alopecia areata in their sample.[73] These findings are indicative —though not conclusive—that the prevalence of autoimmune disease is higher among women with LS than in the general population.[76]

The association with autoimmune disease among male patients with LS is notably weaker. One of the larger studies (n = 532) found that 18.9% of women and 5.1% of men had at least one co-occurring autoimmune disorder ($P < .0001$).[74] A study of 329 male patients found autoimmune disease in only 7% of men and women with LS, and numerous studies found little association at all among men.[17,21,68,77] The autoimmune diseases uncovered in these studies among men varied, but included autoimmune

Table 3. Infection and lichen sclerosus

Authors	Year	Sex	#Patients*	Infection Detection Method	Results (pos./tot)	%
				Borrelia Burdorferi		
Ross et al[106]	1990	nr	21	Microscopic sections w/ modified Steiner stain	10/21	48
Dillon et al[107]	1995	nr	10	PCR & electrophoresis, Southern blot	0/10	0
Fujiwara et al[108]	1997	nr	34	PCR & electrophoresis	0/34	0
Colome-Grimmer et al[109]	1997	nr	10	PCR & electrophoresis	0/10	0
Aberer et al[110]	1999	M/F	19	PCR & electrophoresis†	13/19	68
Ozkan et al[111]	2000	nr	12	PCR & electrophoresis	6/12	50
Eisendle et al[112]	2008	M/F	52	PCR & electrophoresis, FFM	FFM: 33/52 PCR: 0/5	63 0
Edmonds et al[113]	2009	M	30	ELISA, IgG Western blot	ELISA: 0/30 Western: 0/30	0 0
				Epstein Barr Virus		
Aide et al[114]	2010	F	34	PCR & electrophoresis	9/34	26
Zhang et al[115]	2016	M	47	Real-time PCR	18/47	38
				Hepatitis C Virus		
Shim et al[116]	2012	M	61	ELISA, ECLIA	0/61	0
				Human Papilloma Virus		
Kiene et al[117]	1991	F	18	PCR & electrophoresis, ISH	4/18	22
Lau et al[118]	1995	M	10	PCR & electrophoresis	0/10	0
Drut et al[119]	1998	M	23	PCR & electrophoresis, ISH	16/23	70
Lerma et al[120]	1999	F	21	PCR & electrophoresis	0/21	0
Regauer et al[80]	2002	F	22	PCR & electrophoresis	8/22	36
Powell et al[121]	2003	F	32	PCR & electrophoresis	8/32	25
Nasca et al[122]	2006	M	46	PCR & electrophoresis	8/46	17
van der Avoort et al[123]	2006	F	10	PCR & reverse hybridization line probe assay	0/10	0
Prowse et al[124]	2008	M	18	PCR & reverse hybridization line probe assay	6/18	33
Aide et al[114]	2010	F	34	PCR & electrophoresis	0/34	0
Guerrero et al[125]	2011	F	21	PCR & electrophoresis, reverse line blot hybridization	5/21	24
Edmonds et al[21]	2012	M	120	Histological section	6/120	5
Guerrero-Setas et al[126]	2013	M	27	PCR & electrophoresis, reverse line blotting	1/27	4
Zhang et al[115]	2016	M	47	Real-time PCR	0/47	0

ECLIA, electrochemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; F, female; FFM, focus-floating microscopy; IgG, immunoglobulin G; ISH, in situ hybridization; M, male; nr, not reported; PCR, polymerase chain reaction.
* Only patients with LS alone included.
† Investigators used a urine sample instead of a tissue biopsy.

vitiligo (8%-12.3%),[55,78] thyroid disease (3.8%-12.5%),[74] and alopecia areata (1.5%-12.3%)[21,55] among others.

Protein targets support the idea of an autoimmune phenotype of disease, the classic example is extracellular matrix protein 1 (ECM1).[5,79] Autoantibodies to ECM1 were found in 74% of a LS patient population of women (n = 86). Other potential markers include T-cell clones, which are found in overabundance in LS patients' tissue.[80] LS patients also have a redundant Th1 response with greater expression of pro-inflammatory cytokines involved in autoimmunity; LS patients have upregulated levels of microRNA-155, which is hypothesized to reduce the regulatory T-cell suppression of CD4+ T-cells and possibly promote fibroblast cell proliferation.[81,82] Cytokines, chiefly interleukin-1 (IL-1) as well as IL-12, IL-2, IL-5, IL-10, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and type I IFN are potentially upregulated in LS.[83]

Finally, occluded exposure of urine to susceptible epithelium may play a central role in the pathogenesis of LS. The skin may have an isotraumatopic response, or the onset of a new skin disorder at the locus of cutaneous trauma.[84] Urine, feces, and other nonspecific[85] liquid irritants in occluded spaces may play an important role in the etiology of LS in both men and women.[86] Anatomically, LS has an unambiguous predilection for genitalia. The rarity of disease in circumcised males,[52,53] the absence of perianal disease in men but the preponderance of perianal disease in women,[21] and the localization of disease to occluded epithelium[62,87] even at the site of perineal urethrostomy all support this hypothesis.[88]

Clinically, preliminary small studies and case reports suggest that men and women diagnosed with LS endorse postmicturition dribbling or exposure to urine (Table 4).[25,61] The isotraumatopic response due to occluded urine also potentially explains the association between LS and higher BMI, as excess adipose tissue and skin can act as a pseudoforeskin in obese patients, regardless of circumcision status.[25] Though a viable component cause, trauma has not

Table 4. Studies of lichen sclerosus examining occlusion and liquid irritants*

Authors	Year	Sex	#Patients	Circumcised (n)†	Site of Involvement	Method of Assessing Irritant Exposure	Irritant (n)	%‡
Owen & Yell[127]	2002	F	7	N/A	Genitals§	Patient report	Urine (7); feces (3)	
Al-Niaimi & Lyon[88]	2013	M/F	12	N/A	Peri-abdominal stoma	Patient report	Urine (12)	
Bunker[61]	2013	M	56	Yes (56)	NR	Patient report	Urine (53)	94.6
Doiron[25]	2017	M	19	Yes (2); No (17)	Genitals & pseudoforeskin	Patient report	Urine (16)	84.2

F, female; M, male; N/A, not applicable; NR, not reported.
* Only studies specifying a liquid irritant reported by or observed in the patient are included.
† Only male circumcision is reported.
‡ If sample is cross-sectional tested for postmicturition dribbling, % reporting.
§ No specific site of genital skin is reported.

been demonstrated to be necessary or sufficient in the etiology of LS.[61]

CONCLUSION

Although the etiology of LS remains unknown, infectious, anti-immune, or chronic irritation may all play a role in its presentation. Future research should explore the intersection of infections, skin microtrauma, and immune dysregulation leading to this disease state. Clinically, LS has the potential to progress to malignancy or cause debilitating changes to normal tissues. Topical corticosteroids are the current mainstay of medical treatment. Surgical therapy should avoid use of genital skin due to the high likelihood of local recurrence. As primary providers of patients with genital LS, urologists must contribute to advancing medical knowledge of this condition and be involved in future research on the topic.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.09.034.

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