Histological Evidence of Urethral Involvement in Male Patients With Genital Lichen Sclerosus: A Preliminary Report

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Purpose: Using pathological examination we evaluated the involvement of lichen sclerosus in urethral strictures in men.

Materials and Methods: We performed an observational, descriptive, retrospective study of patients treated for genital lichen sclerosus who had at least 1 biopsy positive for lichen sclerosus. Study exclusion criteria were malignant penile lesions, incomplete data on personal charts and biopsies negative for lichen sclerosus. Preoperative evaluation included clinical history, physical examination, urine culture, post-void residual urine measurement, uroflowmetry and urethrography. Biopsies were taken from the foreskin, penile skin, glans, urethral meatus, mucosa of the navicularis, and penile and bulbar urethra to confirm the lichen sclerosus diagnosis and spread of the disease through the urethra. Patients were classified into 5 groups by surgical procedure.

Results: Included in the study were 99 patients with a median age of 46 years who were diagnosed with genital lichen sclerosus. Of 274 biopsies 234 (85.4%) were positive for lichen sclerosus. Group 1 included 39 patients who underwent circumcision, group 2 included 15 who underwent meatotomy, group 3 included 15 who underwent navicularis urethroplasty, group 4 included 17 who underwent penile urethroplasty and group 5 included 13 who underwent perineal urethrostomy. Lichen sclerosus was documented by histology in the meatus in 91.5% of cases, in the navicularis in 84.4% and in the penile urethra in 70.6%. All biopsies from the bulbar urethra were negative.

Conclusions: Involvement of lichen sclerosus through the navicularis and penile urethra was documented. No sign of lichen sclerosus was found in the bulbar urethra.

Key Words: urethra; urethral stricture; lichen sclerosus et atrophicus; genitalia, male; pathology

Abbreviations and Acronyms

BXO = balanitis xerotica obliterans

LS = lichen sclerosus

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LICHEN sclerosus is a chronic inflammatory autoimmune skin disease that causes discomfort and morbidity.[1] In 1887 Hallopeau first reported LS and in the urological literature LS was initially reported as being BXO, which was first defined in 1928 by Stühmer.[1,2] Since then, many names have been used to refer to the disorder. In 1995 the American Academy of Dermatology recommended that the term LS be used in future reports.[1,3]

The exact prevalence of LS is unknown, and methods of diagnosis and treatment may differ.[1] LS may cause destructive scarring that can lead to

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urinary and sexual problems, and decreased quality of life. Symptoms are pruritus and soreness, difficulty in retracting the foreskin and a poor urinary stream.[1] Examination shows typical flat, atrophic, ivory to white papules that coalesce in plaques of varying sizes, commonly with a nonretractile prepuce and meatal stenosis.[1,4]

Controversy exists about the incidence of LS involving the anterior urethra in men. The dermatological literature fails to recognize involvement of the anterior urethra in male patients with genital LS.[1,2] In contrast, in 1970 the urological literature began to emphasize urethral involvement in BXO cases.[5] In 1971 Bainbridge et al reviewed the natural history and histological sections in 17 BXO cases, and first emphasized the diagnostic histological feature of the disease in urethral tissue.[6] In 1978 Mallo et al reported 5 cases of BXO, emphasizing urethral involvement with histological findings from the foreskin, meatus and penile urethra.[7] In 1979 Herschorn and Colopinto described a case of biopsy proven BXO that involved the usual areas as well as the anterior urethra.[8] In 1979 Khezri et al reviewed a series of 20 patients with histologically proven BXO.[9] They suggested that urethral involvement is limited to the squamous epithelium of the external urinary meatus and fossa navicularis, and stated that no evidence indicates that associated urethral strictures were also due to BXO.[9] In 1998 Venn and Mundy reported on 114 patients undergoing anterior urethroplasty for nontraumatic conditions.[10] A total of 28 cases (24.5%) of urethral stricture due to LS were identified and histological assessment of the urethra uniformly showed LS characteristics. In 1999 Barbagli et al reported that 31 of 106 patients (29%) who underwent urethroplasty for anterior urethral strictures had a specific pathological diagnosis of LS, which involved the meatus in 19%, navicularis urethra in 16%, penile urethra in 3% and the entire anterior urethra in 52%.[11] Barbagli et al also reported a high incidence of LS in patients with failed hypospadias repair.[12] However, the relationship between LS and anterior urethral stricture remains an open, controversial issue and further investigative studies are mandatory.

We studied male patients treated for genital LS, evaluating anterior urethral involvement by multiple histological biopsies. Our aim was to ascertain the exact site and extension of LS through the navicularis, penile and bulbar urethra.

MATERIALS AND METHODS

We performed an observational, descriptive, retrospective study in consecutive men who were evaluated and treated for genital LS. Study inclusion criteria were male gender, age 18 to 85 years, evaluation and treatment for genital LS, and at least 1 biopsy positive for LS. Exclusion criteria were malignant penile lesions, incomplete data on personal charts and biopsies negative for LS. All data since January 2002 to December 2009 were retrospectively collected.

The study design allowed us to evaluate the exact site and extension of LS through the navicularis, penile and bulbar urethra. Preoperative patient evaluation included clinical history, physical examination, urine culture, postvoid residual urine measurement and uroflowmetry. All patients with a clinical history of urethral manipulation, obstructive symptoms, meatal stenosis and maximum urine flow less than 10 ml per second on uroflowmetry underwent retrograde and voiding urethrography.

In each case multiple biopsies were taken from the genitalia (foreskin, penile skin and glans), urethral meatus and mucosa of the anterior urethra at preoperative investigation or surgical repair, including circumcision, meatotomy or anterior urethroplasty, to confirm the LS diagnosis according to strict pathological criteria, as suggested in the literature.[1,3] Meatal biopsies were taken from the lateral edges, including the urethral mucosa and the glans epithelium. Biopsies of the navicularis, penile and bulbar urethra were taken from the white area of the mucosa, excluding the spongiosum tissue. All biopsies were evaluated by the same pathologist (FM).

LS was defined as an epithelial-stromal lesion characterized by orthokeratotic hyperkeratosis, thinned epithelium with blunting or loss of rete ridges, basal vacuolar change, subepithelial edema and homogenization of collagen with diffuse perivascular lymphocyte infiltrate. Biopsies were fixed in 10% buffered neutral formalin, entirely embedded in paraffin, sectioned on at least 3 levels and colored with hematoxylin and eosin.

Patients were classified into 5 groups by disease site and surgical repair type. Due to the study design, which was nonanalytical and did not include a control group, only descriptive statistical analysis was performed.

RESULTS

A total of 99 men with a median age of 46 years (range 18 to 85) with genital LS were treated. In the 99 patients a total of 274 biopsies were taken from the foreskin, penile skin, glans, urethral meatus, and navicularis, penile and bulbar urethral mucosa at preoperative investigation or surgical repair to confirm the LS diagnosis. Of 274 biopsies 234 (85.4%) were positive for LS and 40 (14.6%) were negative (table 1). Biopsies were positive in the foreskin in 93.2% of cases, penile skin in 91.2%, glans in 91.4%, meatus in 91.5%, navicularis urethra in 84.4%, penile urethra in 70.6% and bulbar urethra in 0% (table 1 and fig. 1). Of the 99 patients 69 (69.7%) had undergone prior surgery of the genitalia and/or urethra.

Group 1

Of the patients 39 (39.3%) with a median age of 42 years underwent a total of 54 biopsies (table 2). The incidence of LS positive biopsies was 96.6% in the

Table 1. *Biopsy site and result*

Site	No. Biopsies	No. LS (%) Pos	No. LS (%) Neg
Foreskin	73	68 (93)	5 (7)
Penile skin	34	31 (91)	3 (9)
Glans	58	53 (91)	5 (9)
Meatus	47	43 (91)	4 (9)
Urethra:			
Navicularis	32	27 (84)	5 (16)
Penile	17	12 (71)	5 (29)
Bulbar	13	0	13 (100)
Totals	274	234 (85)	40 (15)

Table 2. *Patient age and interval between disease/symptom onset and LS histological diagnosis*

Group No. (site)	Median (range)
Age:	
1 (foreskin)	42 (22–85)
2 (meatus)	46 (18–67)
3 (navicularis)	40 (19–68)
4 (penis)	45 (21–67)
5 (panurethra)	59 (40–74)
Interval (yrs):	
1 (foreskin)	0 (0–39)
2 (meatus)	11 (0–45)
3 (navicularis)	13 (0–26)
4 (penis)	14 (3–50)
5 (panurethra)	17 (2–31)

foreskin, 100% in penile skin and 85.7% in the glans. No biopsies were taken from the meatus or urethra. Of the 39 patients 16 (41%) underwent prior surgery, including circumcision, meatotomy, hypospadias repair, dilation or associated treatment. At the time of our evaluation none showed symptoms requiring meatal or urethral manipulation. These patients had undergone circumcision. In this group the median interval between disease/symptom onset and the histological diagnosis of LS was 0 years (range 0 to 39) (table 2).

Group 2

Of the patients 15 (15.2%) with a median age of 46 years underwent a total of 44 biopsies (table 2). The incidence of LS positive biopsies was 100% in the foreskin, 100% in penile skin, 100% in the glans and 86.7% in the meatus. No biopsies were taken from the urethra. Of the 15 patients 11 (73.3%) had undergone prior surgery, including circumcision, hypospadias repair, dilation or associated treatment. At the time of our evaluation they showed symptoms. These patients underwent meatotomy. In this group the median interval between disease/symptom onset and the histological diagnosis of LS was 11 years (range 0 to 45) (table 2).

Group 3

Of the patients 15 (15.2%) with a median age of 40 years underwent a total of 55 biopsies (table 2). The incidence of LS positive biopsies was 87.5% in the foreskin, 66.7% in penile skin, 72.7% in the glans, 100% in the meatus and 86.7% in the navicularis urethra. Of the 15 patients 12 (80%) had undergone

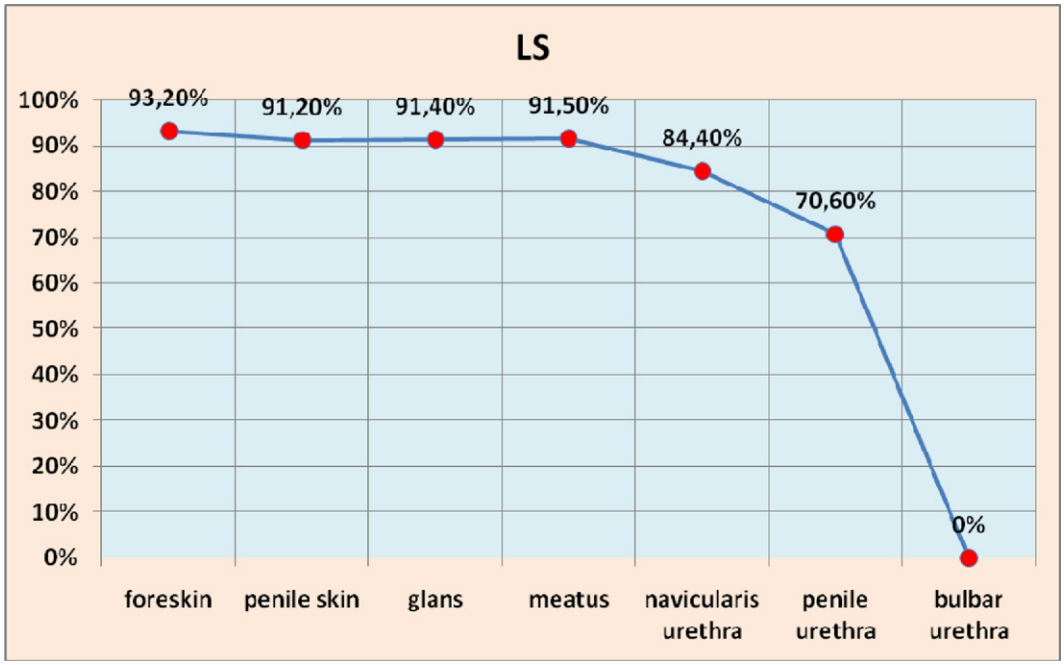

Figure 1. Biopsy sites and results

prior surgery, including meatoplasty, hypospadias repair, dilation or associated treatment. At the time of our evaluation they showed symptoms requiring surgery. These patients underwent 1 or 2-stage navicularis urethroplasty. In this group the median interval between disease/symptom onset and the histological diagnosis of LS was 13 years (range 0 to 26) (table 2).

Group 4

Of the patients 17(17.2%) with a median age of 45 years underwent a total of 82 biopsies (table 2). The incidence of LS positive biopsies was 100% in the foreskin, 87.5% in penile skin, 100% in the glans, 88.2% in the meatus, 82.4% in the navicularis urethra and 70.6% in the penile urethra. All patients had undergone prior surgery, including circumcision, meatotomy, hypospadias repair, dilation or associated treatment. At the time of our evaluation they showed symptoms requiring surgery. These patients underwent 1 or 2-stage penile urethroplasty. In this group the median interval between disease/symptom onset and the histological diagnosis of LS was 14 years (range 3 to 50) (table 2).

Group 5

Of the patients 13 (13.1%) with a median age of 59 years underwent a total of 39 biopsies (table 2). The incidence of LS positive biopsies was 70% in the foreskin, 100% in penile skin, 100% in the glans and 0% in the bulbar urethra. All patients had undergone prior surgery, including circumcision, dilation, urethroplasty or associated treatment. At the time of our evaluation they showed symptoms requiring surgery. These patients underwent perineal urethrostomy for panurethral strictures. Biopsies were taken only in the bulbar urethra since the navicularis and penile urethra were not surgically exposed. In this group the median interval between disease/symptom onset and the histological diagnosis of LS was 17 years (range 2 to 31) (table 2).

DISCUSSION

LS is difficult to manage due to the wide range of clinical presentations, anatomical involvement and surgical options.[13] Involvement of the anterior urethra in male patients with LS always starts at the squamous epithelium of the meatus and fossa navicularis.[9] Of the 45 patients with navicularis (15), penile (17) or panurethral (13) stricture meatal involvement was always present in our series. In 91.5% of the patients meatal biopsies were positive for LS. Also, in the 39 patients with no meatal or urethral involvement 16 (41%) had a history of surgery in the meatal or urethral area, including meatotomy, hypospadias repair, dilation or associated treatment.

Embryology of the glans explains the involvement of the meatus and navicularis tract in LS since the developing glanular urethra involves the preputial folds that fuse to the genital folds.[14,15] In some patients the disease extends through the penile urethra. In our series LS was documented in the penile urethral mucosa in 12 of 17 men (70.6%). However, LS was evident in 14 of these 17 patients (82.4%) in the navicularis mucosa and in 15 (88.2%) in the urethral meatus, showing evidence of descending urethral involvement from meatus to proximal urethra. It is not clear why in some patients the entire anterior urethra was involved with the disease, showing the radiological features of panurethral stricture (fig. 2).[16]

It was suggested that panurethral strictures in patients with LS are caused by the trauma of repeat dilatation and some groups thought that no evidence indicates that associated urethral strictures proximal to the fossa navicularis are due to LS.[6,9] Venn and Mundy suggested that urethral involvement is caused by BXO.[10] We investigated whether 60 patients with LS urethral strictures had other possible diseases or conditions in the clinical history that could be recognized as causing urethral stricture. Only 14 patients (23.3%) had a history of a clinical condition that may be considered to cause stricture, such as hypospadias repair in 8, transurethral prostate resection in 3, catheterization in 2 and cardiovascular surgery in 1. Of the 60 patients with urethral strictures associated with histologically proven

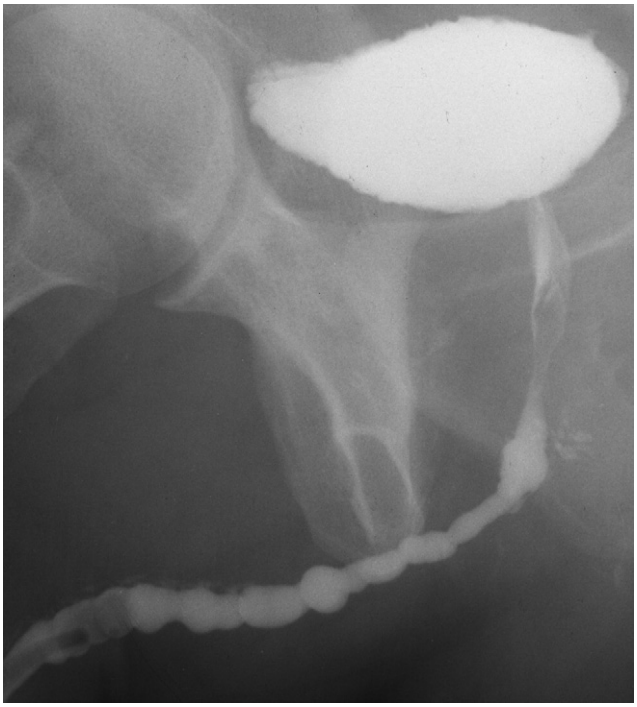

Figure 2. Retrograde urethrogram shows panurethral stricture

LS 76.7% showed no disease or condition recognized as causing urethral stricture. We documented histological LS in the meatus in 91.5% of cases, navicularis urethra in 84.4% and penile urethra in 70.6% (fig. 3, *A* and *B*). However, all biopsies from the bulbar urethra were negative for LS despite radiological panurethral strictures (figs. 2 and 3, *C*). In the bulbar urethral mucosa the histological alteration present in all biopsies was squamous metaplasia of the hyperplastic and orthokeratotic type (fig. 3, *C*).

LS is a disease of the epidermidis and in the mucous membrane it is always preceded by epidermization. When the distal urethra is lined by normal, pseudo stratified cylindrical epithelium, LS is never involved. To our knowledge the pathogenesis of LS spread into the urethra remains unknown and we can only provide unsupported speculation. The epithelium must become squamous through a metaplastic process due to chronic irritation. If irritation continues, the metaplastic squamous epithelium becomes hyperplastic and hyperorthokeratotic (epidermis-like or epidermized). Only then does LS eventually involve the distal urethra in a contiguous, slow manner from preexisting LS of the glans and/or urethral meatus (fig. 3, *A* and *B*). LS was never found to involve the bulbar urethra in our opinion since diffuse epidermization of the penile tract induces severe symptoms that prompt therapeutic intervention before LS may involve the proximal tract.

Our study provides useful data on the natural history of LS and its management. In all patients disease/symptom onset started many years before our evaluation (table 2). However, only 3 patients (3%) had undergone biopsy to ascertain the correct diagnosis. The median interval between disease/symptom onset and our histological diagnosis of LS was 0 years (range 0 to 39) in patients with only genital involvement, and 13, 14 and 17 years in patients with navicularis, penile and panurethral involvement, respectively. This suggests the hypothesis that panurethral strictures develop in patients with long-standing disease who were treated for many years with dilation or another therapy (table 2). The median age of patients with early disease and no urethral involvement in group 1 was lower than the median age of patients with long-standing disease in group 5 (42 vs 59 years). This suggests the hypothesis that more than 10 years are needed for the disease to progress through the entire urethra (table 2). In our patients with LS delayed diagnosis was evident since an incorrect disease was diagnosed and the risk of disease evolution with time through the entire anterior urethra was underestimated.

In patients with genital LS meatal involvement should be considered a negative prognostic factor as far as proximal urethral involvement is concerned and patients with meatal stenosis require careful followup. We speculate that the urinary obstruction caused by distal, meatal or navicularis stenosis may promote epidermization of the urethral mucosa, creating the basis for LS to diffuse in the remaining tract. However, further studies are mandatory to confirm this hypothesis.

Unfortunately in our study biopsy was not standardized. However, we are now organizing a new standard protocol to better collect and evaluate the role of histological biopsies to predict the negative evolution of the disease. Another 2 weaknesses of our study are its retrospective nature and its single institution setting.

CONCLUSIONS

In patients with genital LS involvement of the external urinary meatus is a prognostic factor for spread through the navicularis and penile tract. Based on our retrospective data it appears that more than 10 years are required to progress but more data are needed to confirm this. Nevertheless, it is not possible to confirm LS in the bulbar urethra using histological biopsy despite radiological evidence of a panurethral stricture.

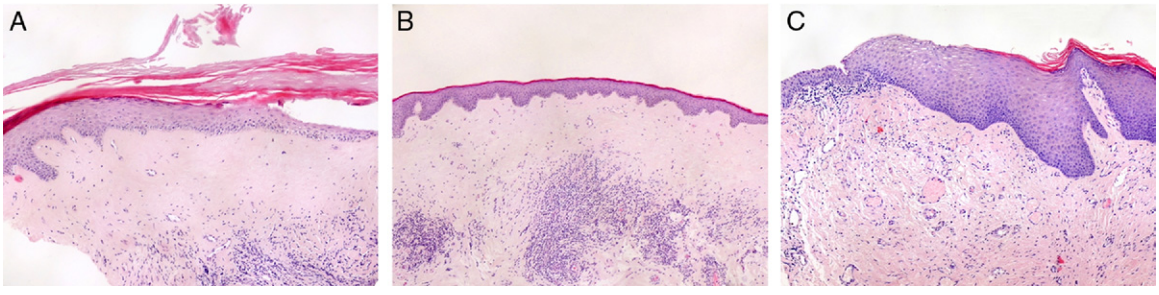

Figure 3. *A*, epidermized navicularis urethral mucosa. LS similar to cutaneous counterpart. Reduced from ×20. *B*, epidermized penile urethral mucosa. LS similar to cutaneous counterpart. Reduced from ×10. *C*, bulbar urethral mucosa. Transition from normal stratified cylindrical epithelium (left) through squamous nonkeratinizing metaplastic epithelium to keratinizing squamous metaplastic hyperplasia (right). Reduced from ×10.

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