Urethral lichen sclerosus under the microscope: a survey of academic pathologists

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Introduction: *Given the poor understanding of the pathophysiology of genital lichen sclerosus (GLS) and a lack of accepted definitive diagnostic criteria, we proposed to survey pathologists regarding their understanding of GLS. We hypothesized that significant disagreement about GLS will exist.*

Materials and methods: *All urologists participating in the Trauma and Urologic Reconstruction Network of Surgeons identified genitourinary (GUP) and dermatopathologists (DP) at their respective institutions who were then invited to participate in an online survey regarding their experience with diagnosing GLS, GLS pathophysiology and its relationship to urethral stricture disease.*

Results: *There were 23 (12 DP, 11 GUP) pathologists that completed the survey. The most agreed upon criteria for diagnosis were dermal collagen homogenization (85.7%), loss of the normal rete pattern (33.3%) and atrophic epidermis (28.5%). No pathologists believed GLS had an infectious etiology (19% maybe, 42% unknown) and 19% believed GLS to be an autoimmune disorder (42% maybe, 38% unknown); 19% believed LS to be premalignant, but 52% believed it was associated with cancer; 80% believed that LS could involve the urethra (DP (92%) versus GUP (67%); p = 0.272). Of those diagnosing urethral GLS, 80% of DUP believed that GLS must first involve the glans/prepuce before involving the urethra, while all GUP believed that urethral disease could exist in isolation (p = 0.007).*

Conclusions: *There was significant disagreement in this specialized cohort of pathologists when diagnosing GLS. A logical first step appears to be improving agreement on how to best describe and classify the disease. This may lead to improve treatments.*

Key Words: urethral stricture disease, genital lichen sclerosus, histopathology

Introduction

Male genital lichen sclerosus (GLS) is a relatively uncommon dermatologic condition, with a prevalence estimated to be 70/100,000 men.[1] Historically known as balanitis xerotica obliterans (BXO), men with GLS will often first present with sexual and/or urinary sequelae.[2-5] GLS is associated with both urethral stricture disease (USD), developing in nearly 20% of cases,[3] and penile cancer, developing in nearly 5% of all male GLS cases.[6] USD associated with GLS can be particularly difficult to manage, involving large segments of the penile urethra, and in many cases, requiring permanent urinary diversion.[7]

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The association of GLS and USD is well described in the urologic literature. The conventional wisdom amongst urologists is that GLS starts as a dermatologic condition of the distal penis (glans, prepuce), and then migrates proximally in a step-wise fashion down the urethra from the meatus to the bulbar urethra, with the membranous urethra generally being spared.[2,8] However, pathologically, this orderly progression has not been confirmed, nor has urethral GLS been well described in the pathology literature. Additionally, the possibility of skip-lesions (i.e. LS lesions that involve only the bulbar urethra without a cutaneous component) has recently been suggested, disrupting our current hypothesis of disease progression.[9]

To our knowledge, there is no formal consensus on diagnostic criteria necessary for the diagnosis urethral lichen sclerosus (LS). While cutaneous GLS is often treated with Class 1 topical steroids, such as clobetasol and halobetasol,[10] with moderate effectiveness, their usefulness within a GLS affected urethra is largely unknown.[11] However, if urethral GLS is indeed pathologically similar to its dermatologic counterpart, then treatment algorithms for this often surgically recalcitrant disease may need to include more local and systemic therapies, either as adjuncts or alternatives to surgical methods. Thus, a better understanding of the pathology of urethral stricture disease will be vital to progress in the treatment of GLS.

The purpose of this study was to establish the current pathologic understanding of urethral GLS from the perspective of the pathologist. Considering the relative rarity of the disease process, we hypothesized that significant heterogeneity in understanding of urethral USD would exist amongst pathologists in regards to current terminology, diagnostic criteria, grading, pathogenesis and conditions associated with GLS. Furthermore, we hypothesized that a comparison of dermatopathologists (DP), a group familiar with dermatologic pathology, to genitourinary pathologists (GUP), a group presumably more familiar with oncologic pathology, but generally asked to review that pathology of urethral specimens, would yield further insights into deficiencies in our working knowledge of the disease.

Materials and methods

Study participants

This study surveyed genitourinary (GUP) and dermatopathologists (DP) from academic institutions associated with the Trauma and Urologic Reconstruction Network of Surgeons (TURNS; www.turnsresearch.org). All pathologists that were invited to participate in the study had worked directly with the institution's urologist, and thus, were presumed to have some familiarity with GLS. However, the nature and purpose of the questionnaire was not directly discussed with the pathologists prior to administration.

Questionnaire

The questionnaire was developed and tested by the study authors' on pathologists from their home institution. Individual questions were then modified for clarity and content before being distributed to the 11 other TURNS institutions pathologists'. Pathologists involved in questionnaire development were not included in the final study population.

Questions were circulated to the study pathologists using SurveyMonkey (SurveyMonkey Inc., Palo Alto, CA, USA, www.surveymonkey.com) and all data were stored, and then extracted, from the SurveyMonkey web-based server at the completion of the survey period. The questionnaire used skip logic when applicable, and thus, not all 18 questions were answered by every participant. Specific questions can be found in Table 1. Question categories included 1) provider/pathologist demographics 2) terminology, diagnostic criteria, and grading for genital lichen sclerosus (GLS) 3) etiology of GLS and 4) associations of GLS with penile and urethral carcinoma.

Statistical analysis

Answers from all participants were compiled utilizing descriptive statistics. We then compared cumulative data from dermatopathologists (DP) and genitourinary pathologists (GUP) utilizing both chi-squared analyses and T-testing for categorical and continuous variables respectively. All statistics were performed using Graph Pad Prism (GraphPad Software, Inc., La Jolla, CA, USA, www.graphpad.com) with significant differences being determined when p values were found to be < 0.05.

Results

Pathologist characteristics

Of the 28 pathologists initially approached to complete the survey, 21 agreed to participate and 21 completed the entire survey, of whom 12 were dermatopathologists (DP) and 9 were genitourinary pathologists (GUP). The mean number of years in clinical practice for the study participants was 12.2 (± 8) years.

Making the diagnosis of genital lichen sclerosus

The terminology utilized to described lichen sclerosus of the genitalia in pathology reports remains balanitis

TABLE 1. **Pathologist survey questions on urethral lichen sclerosus**

1	How many years have you been in clinical practice?
2	Do you have subspecialization in dermatopathology? (yes/no)
3	Do you have subspecialization in urologic pathology? (yes/no)
4	Which histopathologic findings are important to make the diagnosis of lichen sclerosus? 1) Hyperkeratosis 2) Atropic dermatitis 3) Loss of normal rete pattern 4) Plugging of the follicular Infundibulum 5) Vacuolar degeneration of basal layer 6) Epidermal/dermal clefting 7) Dermal collagen collagen homogenization 8) Lichenoid lymphocytic infiltrat 9) Subepidermal bullae 10) Other
5	Which histopathologic findings must be present to make the diagnosis of lichen sclerosus? (see list above)
6	When diagnosing genital lichen sclerosus, do you still utilize the terminology balanitis xerotica obliterans (BXO)? (always, never, sometimes)
7	When diagnosing genital lichen sclerosus, is the clinical history necessary? (yes, no, maybe)
8	When diagnosing genital lichen sclerosus, do you ever assign a grade to the severity of the condition? (yes, no)
9	Do you believe genital lichen sclerosus to be a premalignant lesion? (yes, no, no but associated with cancer)
10	Do you believe genital lichen sclerosus to have an infectious etiology? (yes, no, maybe, unknown)
11	Do you believe genital lichen sclerosus to have an autoimmune etiology? (yes, no, maybe, unknown)
12a	Can genital lichen sclerosus involve the urethra? (yes, no)
12b	If you do not believe that genital lichen sclerosus can involve the urethra, please describe why.
12c	If you do…, do you use different grading criteria when making the diagnosis? (yes (specify), no)
12d	If you do…, does urethral epithelium require metaplasia to squamous epithelium prior to converting to lichen sclerosus? (yes, no)
12e	If you do…,do you believe that the proximal urethra can be involved without first affecting the glans and meatus (i.e. skip lesions in the urethra)?

xerotica obliterans (BXO) in over 90% of pathologists surveyed, with 55% stating they "always" used this term. The clinical history (e.g. statement of "whitish skin of the genitalia", "phimosis of the foreskin") was necessary to make the diagnosis of GLS in 14.3% of those surveyed, with an additional 47.6% stating that the clinical history is sometimes useful. The pathologic findings that were deemed important in making the diagnosis of GLS can be found in Figure 1. Note, there were no criteria that all pathologists agreed upon, though dermal collagen homogenization (95%) was the most commonly cited finding, followed by lichenoid lymphocytic infiltrate (86%). Similarly, there was significant heterogeneity, and no consensus, on criteria

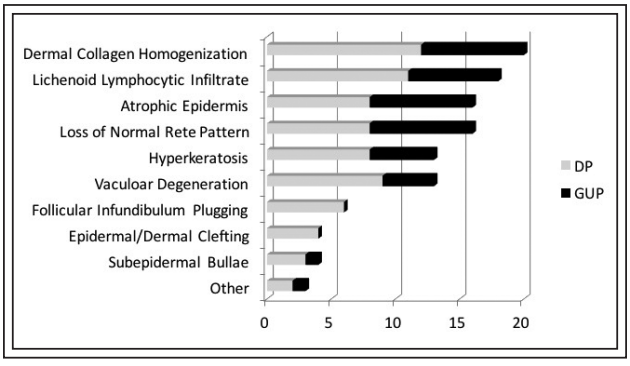

Figure 1. Answers provided by dermatopathologists (DP, grey) and genitourinary pathologists (GUP, black) when asked the question "Which Histopathologic Findings are Important to Make the Diagnosis of Lichen Sclerosus?"

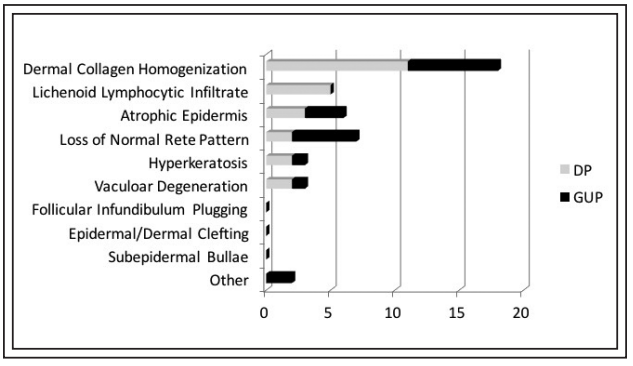

Figure 2. Answers provided by dermatopathologists (DP, grey) and genitourinary pathologists (GUP, black) when asked the question "Which Histopathologic Findings Must be Present to Make the Diagnosis of Lichen Sclerosus?"

that must be present to make the diagnosis, Figure 2, though dermal collagen homogenization was required for the diagnosis in 86% of participants.

Lichen sclerosus and urethral stricture disease

Only 81% of the pathologists believed that LS could involve the urethra. Of those pathologists that did not diagnose urethral LS, the most common reason provided by pathologists was "I have never personally seen this (19%)," followed by "LS is a dermatologic condition (4.8%)".

Of the pathologists that believed that GLS could involve the urethra, 17.6% noted that they utilized different criteria for diagnosis of urethral involvement, examples including "stricter criteria" would be necessary due to disease rarity and the need for "vacuolar interface changes" to distinguish from lichen planus. A slight majority (53.3%) reported that urethral involvement is always preceded by glans/prepuce involvement (i.e. step-wise progression down the urethra was necessary). Less than half (46.7%) felt that squamous metaplasia was a necessary pathologic step prior to urethral LS conversion.

Lichen sclerosus pathophysiology

The etiology of GLS was most commonly reported as unknown (42%). However, 20% believed it was an autoimmune disease with an additional 40% stating it "might" be autoimmune and 20% stating it "might" be infectious.

The majority (81%) did not believe that GLS was a premalignant lesion. However, a majority (52.4%) believed GLS to be associated with penile and urethral cancer.

Dermatopathologists versus genitourinary pathologists

Nearly 20% of DPs believed the LS could "skip" to the bulbar urethra without first affecting the penile skin, versus 0% of GUPs ($p < 0.0001$). DPs were significantly more likely to state that the diagnosis required plugging of the follicular infundibulum and lichenoid lymphocytic infiltrate versus GUPs ($p < 0.01$).

Discussion

The purpose of this study was to understand the histopathology of urethral GLS from the perspective of the pathologist. Our study hypothesis, which stated that we would expect to find significant heterogeneity amongst pathologists in their understanding of urethral lichen sclerosus, was largely supported by the study results. The urologic dogma that states LS can directly affect the urethra and progresses in a step-wise fashion down the urethra from distal to proximal,[8] was not uniformly agreed upon by our pathology colleagues. The significance of these findings is not immediately clear – but regardless, either the urologic understanding of GLS is incorrect, it is incomplete, or urologists in general are doing a poor job of communicating their clinical observations with urethral GLS with our pathologists. Either way, we believe the findings confirm the need to study the histopathology of the urethral stricture disease in more detail such that a common nomenclature can be developed to aid in further disease study.

The pathologists in this study did not agree on any absolute diagnostic criteria for GLS. Rather, it seems that, as is the case with many histopathologic diagnoses, pattern recognition, and perhaps even documented clinical history (as was said by over 60%), is key. The apparent disagreement may also have to do with the recognition that LS histopathology differs in its acute and chronic phases.[6] At disease onset, dermal edema is associated with band-like lymphocytic infiltration, which many pathologists believe to be auto-immune related (over 60% in this study). This is generally followed by progressive hyperkeratosis and dermal homogenization and thickening. In the chronic, formed lesions, the epidermis becomes thinned and cellular activity becomes more scant, though chronic inflammation is generally still present.[6] Thus, the phases of severity seen in lichen sclerosus may preclude pathologists from committing to definitive criteria.

Importantly, pathologists did not uniformly agree that GLS could affect the urethra. Reasons provided by these pathologists were mostly due to a lack of direct experience with the condition (e.g. 19% reported they had never seen it). This finding was surprising given that all surveyed pathologists work directly with TURNS urologists, all of whom manage GLS related USD. In addition, there are a multitude of studies in the urologic literature that seem to document urethral involvement.[8,9,12-17] However, review of these studies reveals that most were performed retrospectively and the diagnosis was made only after the pathologists were instructed to directly look for it. For example, in the Liu et al study, the incidence of bulbar LS increased from 7% to over 40% after re-review of the pathology when the researchers specifically asked the pathologists to look for characteristics consistent with lichen sclerosus (though not necessarily diagnostic of LS)[9]. Similarly, in the Barbagli study, only patients with biopsy confirmed cutaneous lichen sclerosus were analyzed, which undoubtedly influenced the pathologist's interpretation of the urethral pathology.[8]

Despite the disagreement in nomenclature, there appears to be a clear, and strong, association (if not evidence of direct involvement) with GLS and urethral stricture disease of the distal urethra. The urethral meatus and fossa navicularis are both lined by non-keratinizing squamous epithelium and should theoretically be susceptible to cutaneous diseases. The main controversy seems to be in the urethral segments proximal to these areas. The penile and bulbar urethra are lined by pseudo-stratified columnar epithelium and thus, their direct involvement with a cutaneous condition seems less likely. However, squamous metaplasia is known to occur proximal to areas of urethral stricture, likely the result of high-pressure voiding, and this has been postulated as a potential precursor to LS proximal migration. The survey results showed that nearly half of the pathologist agreed that this change must occur prior to LS development and migration. The cell-to-cell bonds of the metaplastic tissue are less secure and weaknesses that develop in the epithelial lining may allow for the extravasation of urine into the subepithelial tissue, leading to inflammation and fibrosis – a mechanism first proposed in 1976 for gonoccocal USD,[18] though never confirmed. These micro-traumas may also be responsible for the Koebner phenomenon by which the spread of LS has been postulated.[6,19-21] The clinical case depicted in Figures 3 and 4 highlight a classic case of end-stage lichen sclerosus of unknown pathophysiology.

Ultimately, a pathologic diagnosis is only as good as its ability to direct medical and/or surgical treatments. In the case of urethral GLS, it would thus be reasonable to ask why urologists, believing these strictures to be caused by lichen sclerosus, do not treat the disease like a dermatologist might. The mainstay of treatments for cutaneous GLS remain topical, and sometimes systemic, corticosteroids and immunomodulators.[6] Surgical excision is rare, and is generally reserved for women with recalcitrant labial adhesions leading to sexual dysfunction.[22] However, with the exception of a few reports advocating intraurethral steroid use for GLS related USD,[11,23] the urologic literature is mostly full of surgical outcomes and technique papers.[3,24] Recent reports of associations with urethral GLS and systemic disease have forced us to rethink our current treatments for this disease and its pathophysiology,[25,26] though a subsequent AUA survey would suggest that overall, few changes have been made in how we treat this often debilitating disease process over the past decades,[27] other than perhaps the acknowledgement that urinary diversion often results in the best clinical outcomes (though rarely a cure).[7] It seems likely that identification of the disease earlier in the process by urologists, primary care physicians and dermatologists through education initiatives, followed by aggressive management of the meatal and fossa navicularis

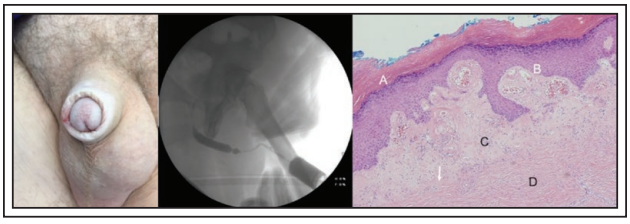

Figure 3. Patient with classic signs of external genitalia lichen sclerosus (left). Retrograde urethrogram depicts pan-penile urethral stricture disease (middle). Biopsy taken from the proximal urethra, performed at the time of perineal urethrostomy, shows findings consistent with lichen sclerosus (**A:** hyperkeratosis; **B:** Thinning of epidermis with squamous metaplasia and loss of rete testis; **C:** Homogenization of dermal layer with chronic inflammation; **D:** Normal dermis).

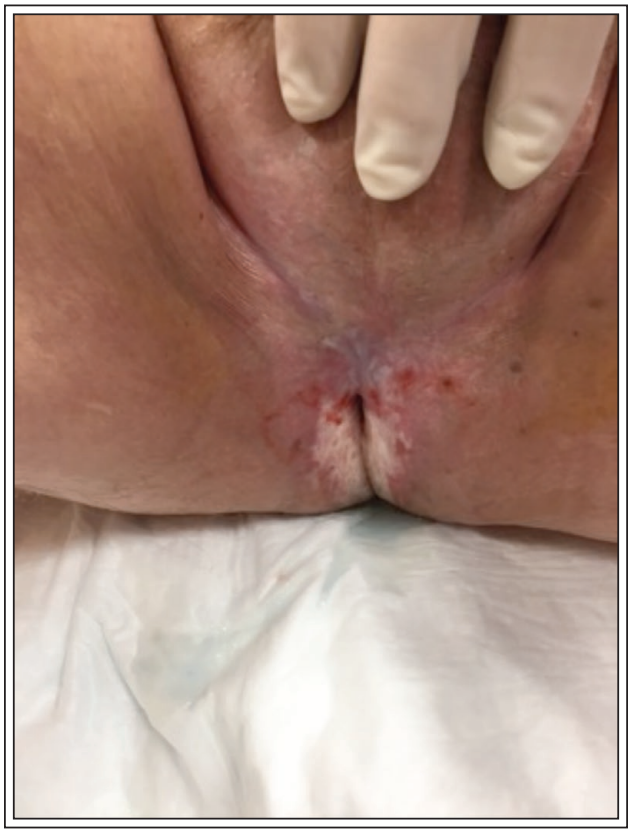

Figure 4. Patient from Figure 3 after one-year of perineal urethrostomy, showing signs of perineal skin involvement. Notably, the urethrostomy remained patent.

disease processes, may offer the best chance of making an immediate impact.

The study was limited by the fact that only pathologists working directly with reconstructive urologists, and thus thought to be familiar with the disease process, were included, though this likely biased the responses toward more familiarity. In addition, these answers were provided in isolation and without discussion. A panel discussion with multiple pathologists discussing these questions likely would have led to a greater consensus. Overall, this study confirmed our hypothesis about the lack of clarity, and significant confusion, in regards to the LS involvement of the male urethra. To advance the field, we must first develop, and then share, a common nomenclature. Steps towards nomenclature development on the urologist's end might include development of a standardized method of urethral tissue collection, in terms of operative, and even preoperative, biopsies for all urethral strictures. This has been suggested previously but not formally implemented.[8] On the pathologist's end, a standardized analysis of the strictured urethral tissue, specifically looking at the degree and type of inflammation, evidence of autoimmunity, degree and type of metaplasia and cellular activity, would help delineate pathophysiology. As the etiology of urethral stricture disease is unknown in nearly half of men with the disease, a better pathologic understanding of the condition may lead to novel, non-surgical treatments.

Conclusions

The heterogeneity in understanding amongst pathologists regarding genital lichen sclerosus involvement of the urethra was considerable. Disagreement exists in the criteria necessary for diagnosis, the ability to involve the urethra, its etiology and mechanism of proximal migration down the urethra. Improvement in treatments for this debilitating condition will only come with a better understanding of its pathophysiology, necessitating a standardized nomenclature agreed upon by both urologists and pathologists. □

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