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Lesson 14
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Male Genital Lichen Sclerosus and Urethral Stricture Disease*

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to recognize the presentation and sequelae of genital lichen sclerosus in males, its role in urethral stricture disease, and the various surgical and non-surgical treatment options available.

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Disclosures: Nothing to disclose

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***This AUA Update addresses the Core Curriculum topics of Urologic Infections, and the American Board of Urology Modules on Infection and Andrology, and Neurogenic Bladder, Voiding Dysfunction, Female Urology, BPH and Urethral Stricture.**

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INTRODUCTION

Lichen sclerosus, previously known as balanitis xerotica obliterans, is a chronic inflammatory, scar forming dermatologic disease that predominately affects the genitalia. **In males, genital LS may involve the prepuce, glans and/or penile shaft skin resulting in a spectrum of genital skin disease.** Depending on the severity of genital LS, the clinical sequelae may be pathological phimosis, adhesions of the penile skin to the glans and frequent skin tearing with erections, and/or acquired buried penis. **LS can also lead to significant urethral stricture disease.** The spectrum of lichen sclerosus urethral stricture disease is highly variable and ranges from simple meatal stenosis to more proximal USD that is frequently panurethral in nature. The wide range of clinical presentation of males with LS can make management challenging for the urologist, especially with increased disease severity. We describe the epidemiology, etiology and pathophysiology; presentation, diagnosis and sequelae; and management of genital and urethral LS to provide knowledge for improved diagnostic competence and appropriate treatment decisions for this complex disease process.

EPIDEMIOLOGY

The true prevalence of LS is difficult to define and likely underreported due to asymptomatic or minimally symptomatic disease in many cases, as well as a lack of provider recognition and familiarity with the diagnosis. The prevalence is classically reported to be between 1/300 to 1/1000 persons based on a study of a cohort of patients referred to a community based dermatology clinic.[1] The estimated incidence in males is 0.0014% to 0.07% based on 2 large retrospective studies in equal access health care system environments.[2, 3] **Although LS occurs in males and females, the reported female-to-male ratio is between 3:1 and 10:1**.[4] In females a bimodal pattern is described with peaks seen in prepubertal and postmenopausal years.[5] In males the age at presentation is reported to be highest in the third through sixth decades of life, although LS is diagnosed in patients of all ages including the pediatric and elderly populations.[2, 3, 5]

ETIOLOGY AND PATHOPHYSIOLOGY

The etiology of LS is poorly understood. It is clear that chronic inflammation and irritation play a role in the development and progression of the disease but unlike other genital dermatologic conditions such as lichen planus, LS results in more severe scar formation eventually leading to permanent skin changes over time.

Chronic irritation/trauma. A well-known dermatologic process called the Koebner phenomenon describes the development of skin lesions along previous sites of trauma and has been hypothesized as a possible cause of LS migration proximally in the urethra in males with LSUSD.[6, 7] Related to this finding is the idea that repeated exposure of susceptible epithelium in occluded spaces to urine, feces and other irritants may play a key role in the development of LS.[8] Another described theory is a 2-hit hypothesis for LSUSD development and progression.[9] The proposed mechanism requires a physical insult to the urethra and/or local infection (hit 1) in the setting of a genetic or acquired inflammatory or autoimmune predisposition (hit 2).

Inflammation. **A systemic pro-inflammatory state likely plays an active role in the development of clinically significant LS.** Previous studies have shown a relationship between LS and certain medical comorbidities such as obesity, diabetes mellitus, hypertension, hyperlipidemia and tobacco use.[8-11] These conditions are known to be associated with acquired autoimmune antibodies and chronic inflammation, and may act as important risk factors for genital and urethral LS. We recently published data comparing protein expression in LSUSD to non-LSUSD and found that the LS group had statistically significant increased levels of inflammatory markers in the tissue specimens, specifically CD8 and CCL-4.[12] Additionally, TNF alpha and IgG4 were only found in LS stricture samples due to LS.

Infection. Previous studies for a possible infectious cause have focused on such infections as Borrelia burgdorferi, Epstein Barr virus, hepatitis C virus and human papillomavirus.[8] We also found that Epstein Barr virus RNA was seen in significantly more LS vs non-LS samples (37% vs 10%, p=0.024).[12] Additionally, Block-like p16, a surrogate for high risk human papillomavirus, and varicella zoster virus were found only in LSUSD samples, although both were rare. Association of these infections with LS is highly variable across the literature, and evidence is currently insufficient to suggest LS has a clear infectious cause. However, our pilot study suggests that future work should evaluate infection as a component of a multi-hit etiology for the development of LS.

Genetics. A familial component is well documented in female LS. In a study of more than 1000 female patients with a diagnosis of vulvar LS 12% had a family history positive for LS.[13] This subset of patients belonged to 95 families indicating that a genetic component is likely involved. The majority of genetics research to date has focused on human leukocyte antigen genotypes. HLA tissue typing of 58 males with LS was compared to that of 602 controls.[14] The LS group showed increased frequency of HLA-DR11, HLA-DR12 and HLA-DQ7. HLA-DQ7 occurs more frequently in male and female LS. To date, no clear causative genetic profile has been identified.

Autoimmunity. There is stronger evidence to suggest an autoimmune association with LS in females than in males. A classic study favoring a potential autoimmune cause revealed evidence of positive immunoreactivity to extracellular matrix protein 1 in the serum of 74% of females with LS compared to 7% of controls.[15] In a retrospective study of more than 500 patients the prevalence of autoimmune diseases and serological parameters indicative of autoimmunity were compared in male and female patients with LS.[16] Female LS showed a significantly increased association with at least 1 autoimmune disease compared to male LS (OR 4.3, 95% CI 1.9–9.6, p <0.0001). This same study indicated that female LS was more commonly associated with autoimmune thyroid diseases (OR 4.7, 95% CI

ABBREVIATIONS: LS (lichen sclerosus), LSUSD (lichen sclerosus urethral stricture disease), LUTS (lower urinary tract symptoms), USD (urethral stricture disease)

1.8–11.9, p <0.0002), antithyroid antibodies (OR 2.7, 95% CI 1.1–6.5, p=0.023) and elevated autoantibodies (OR 4.1, 95% CI 1.9–9.3, p <0.0001) than male LS. Previous literature has also noted LS to be associated with other autoimmune disorders such as vitiligo, alopecia areata and pernicious anemia.[17]

PRESENTATION

Many cases of genital LS can be asymptomatic or minimally symptomatic. As urologists, we typically see these patients once the disease has become symptomatic, and so it is important to become familiar with the common associated symptoms and exam findings. A retrospective review of more than 500 patients with LS showed the disease to be limited to the foreskin/glans in 57% and the meatus in 4%, while urethral involvement was seen in 20%.[18,19] Additionally, genital involvement is reported to be at least 5 times more common than extragenital involvement.[20]

Male genital LS. **The typical dermatologic findings include white or gray discolored and atrophic appearing genital skin. There can be evidence of tissue scarring and irritation, including induration, excoriations and fissures, and tissue fusion/adhesions, which can be bothersome to patients (fig. 1). Sexual dysfunction may also occur, such as worsening pain with erections due to the tearing of skin at areas of ulcerations or fusion/adhesions of the skin to the coronal sulcus.**

If LS progresses to pathological phimosis and eventually acquired buried penis, many of these patients will have significantly diseased and disfigured penile skin (fig. 2). Although it was historically believed that childhood circumcision was protective against LS and previous studies have shown a higher risk of LS in uncircumcised males,[21] we and others have commonly seen genital LS with and without USD in previously circumcised males, notably in the acquired buried penis population.[9] It is unclear if LS is the inciting disease causing acquired buried penis or the chronic moisture and inflammation from penile concealment or a combination of both that results in LS of the genital skin. Because of the penile concealment, those with acquired buried penis often have bothersome urinary symptoms, recurrent urinary tract infections, difficulty with genital hygiene, recurrent genital/inguinal infections and inability to engage in sexual activity.[22] Additionally, acquired buried penis presents with concomitant USD in 31% to 47% of cases, and thus careful evaluation of this population is required for optimal management.[23-25]

Figure 1. Male genital LS with white skin changes and tissue fusion.

Figure 2. LS in acquired buried penis.

LS urethral stricture disease. LS has been reported to be the etiology in 13% to 14% of patients with known USD.[26,27] **Many males will have urethral disease limited to the meatus and/or fossa navicularis but the disease can extend more proximally throughout the bulbopendulous urethra up to and involving the bulbomembranous urethra.** LS is the most common etiology of panurethral strictures in many parts of the world (fig. 3).[28] Although skip lesions and isolated USD without distal involvement have been reported, the disease usually progresses in a distal to proximal fashion through the urethra.[29] Patients with LSUSD typically present with lower urinary tract symptoms. Contrary to patients with USD from other etiologies, those with LSUSD are more likely to be active tobacco users, and have a higher body mass index, hypertension and longer stricture disease.[9] On physical exam patients will frequently

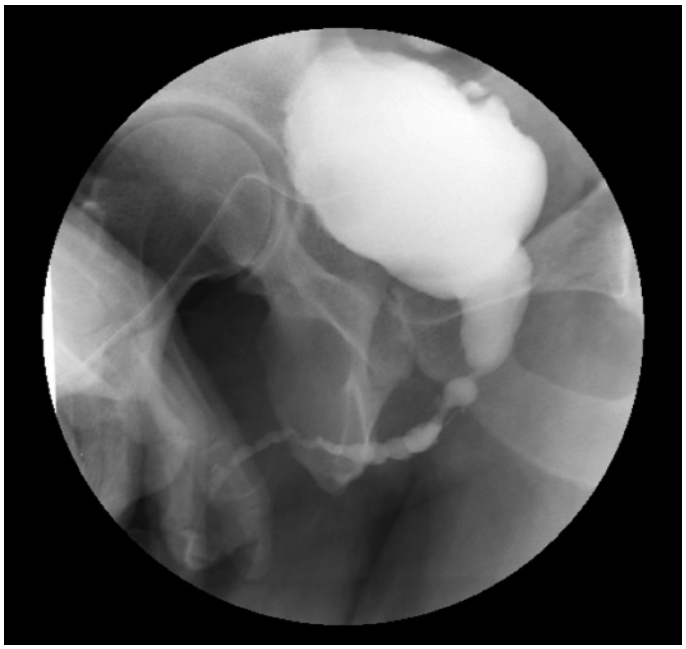

Figure 3. Voiding cystourethrogram shows panurethral stricture.

have external genital LS manifestations that may range from mild perimeatal skin changes to more extensive disease that involves the glans, prepuce and penile shaft skin (fig. 4).

Female LS. **As in males, female LS predominately affects the genitalia, most commonly the vulva, perineum and perianal skin.**[4,30] These patients usually present with genital pruritus that

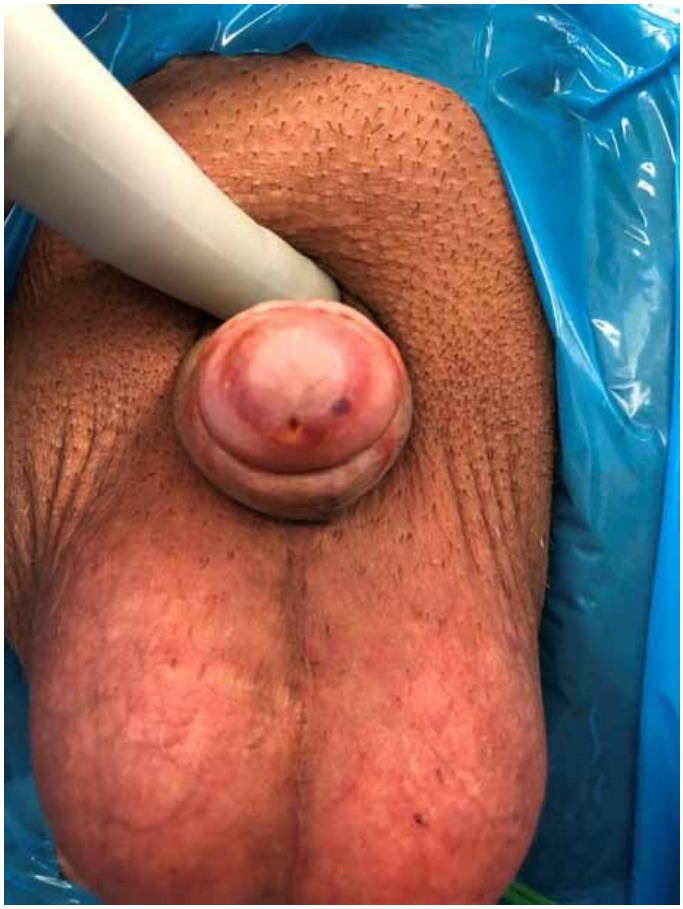

Figure 4. LS of glans with meatal stenosis.

can significantly impact their quality of life. Excoriations and fissuring of the affected tissue are common as in males. Vulvar LS can lead to dysuria and dyspareunia as well. The typical exam findings will show a white plaque, sclerotic in nature, with atrophic wrinkled tissue. The classic described distribution is a figure of eight pattern at the level of the vulva, perineum and perianal area. However, it should be noted that appearance and distribution can be extremely variable in female LS. If left untreated, LS can lead to permanent scarring and deformation of the vulva, and stenosis of the vaginal introitus.

DIAGNOSIS

The diagnosis of LS can only be confirmed on pathological biopsy, despite a lack of accepted definitive diagnostic criteria. A recent survey of 23 academic genitourinary and dermatopathologists resulted in significant disagreement in diagnosing genital LS, which speaks to its complexity and the need to improve how we classify the disease.[31] Nevertheless, the typical clinical exam findings previously described can provide confidence in a sound clinical diagnosis. We do not routinely perform pathological biopsy unless the presentation is atypical or patients do not respond to initial treatment regimens. Differential diagnosis includes other skin disorders such as lichen planus, eczema, psoriasis, scleroderma, leukoplakia, vitiligo, penile intraepithelial neoplasia and squamous cell carcinoma.

One of the most important clinical manifestations of LS is the potential for malignant transformation. Progression to malignancy, most commonly squamous cell carcinoma, is reported in approximately 2% to 8% of males.[19,32] Because this process can occur years after the LS has been treated, we follow many of our patients with LS indefinitely on an annual basis even if the LS has been managed, and is stable and asymptomatic. We strongly encourage self-examinations between clinic visits as well to identify any new or concerning lesions. Similarly, in females the risk of vulvar LS progression to vulvar squamous cell carcinoma is 2% to 6%, and thus careful evaluation and follow-up are needed in this group as well.[30]

An evaluation for LUTS should be performed in all patients who present with LS cutaneous changes of the glans and/or prepuce.[33] We evaluate LUTS using a validated voiding symptom questionnaire including the Urethral Stricture Symptoms and Impact Measure questionnaire[34] and the Urethral Stricture Surgery Patient Reported Outcome Measure questionnaire.[35] If moderate to severe LUTS are present, patients will undergo further objective tests in the form of uroflowmetry and post-void residual measurement.

Urethral imaging is also considered at this point in the form of a retrograde urethrogram with or without a voiding cystourethrogram to further evaluate for LSUSD. **The classic urethrogram finding of LSUSD as it progresses proximally is a narrowed, "beaded" appearance of the urethral lumen (fig. 3)**. Clinic cystoscopy can be performed as part of the urethral evaluation, although in our experience many of these patients have a narrowed urethral lumen that precludes advancement of a 17Fr flexible cystoscope. We find that the retrograde urethrogram with or without the voiding cystourethrogram provides more thorough stricture characteristics and details.

Evaluating patients with acquired buried penis and moderate to severe LUTS for concomitant USD is challenging. If penile concealment is not complete, a retrograde urethrogram can be performed to evaluate for USD. However, the glans frequently

cannot be examined due to the cicatrix of scar concealing the penis. In these situations cystourethroscopy performed with a ureteroscope can be used to evaluate the urethra for USD either prior to or at the time of acquired buried penis repair.

MANAGEMENT

To manage LS effectively, urologists must be comfortable with multiple different treatment options based on the wide spectrum of disease presentation. Previous literature describes the overarching goals of management as alleviation of symptoms, prevention and treatment of USD, and prevention and detection of malignant changes.[33]

Medical management. Genital LS: **In patients with isolated prepuce and glans involvement, circumcision may be effective and adequate management.[19] However, for many patients, topical corticosteroids are considered first line therapy, and topical clobetasol propionate 0.05% is the most common corticosteroid used.** We recommend starting with a twice daily application schedule to the affected prepuce, glans and/or shaft skin (for skin ulcerations or glans adhesions) for 1 to 2 months with gradual tapering thereafter. Topical corticosteroid management can be effective with studies showing up to 90% response rates for genital LS.[36] Even in the absence of urinary symptoms or sexual dysfunction, evidence of LS induced skin changes should be treated early to help stop progression and potentially cause regression of the disease. Topical calcineurin inhibitors, such as tacrolimus 0.1%, have also been effective in the treatment of male genital LS but they are considered off-label use, and topical corticosteroids remain first line therapy.[37]

LSUSD: In the setting of non-obliterative distal LSUSD we routinely offer intraurethral steroid therapy with topical clobetasol propionate 0.05% applied via catheterization of the distal penile urethra for 2 to 3 months, and then tapered thereafter and used intermittently. This treatment has been reported with an 89% success rate at 24.8-month mean follow-up, and is an option for men who are willing and able to perform intermittent catheterization of the distal penile urethra.[38]

Surgical management. LSUSD: Urethral extent and severity can be extremely variable from patient to patient and LSUSD is notoriously challenging to manage surgically with reported stricture recurrence rates as high as 71% following urethroplasty.[39] Patients who present to our clinic with LSUSD are counseled about intermittent catheterization with intraurethral steroids, urethral reconstruction with oral mucosa grafting and perineal urethrostomy. **Oral mucosa grafting is the gold standard for substitution urethroplasty as skin is contraindicated in patients with LSUSD due to the unacceptably high rates of stricture recurrence with skin flaps and grafts.**[40]

There is much debate among reconstructive urologists on the optimal surgical management techniques for LSUSD. For distal USD, a first-stage Johanson approach to achieve an extended meatotomy has shown good results.[41, 42] The key step in this operation is to open the urethra proximally enough in the ventral midline until unaffected healthy mucosal edges are visualized and marsupialized to the adjacent skin edges. We have previously published our algorithm for fossa navicularis strictures.[43] Specifically for LSUSD, if the urethral plate and glans size allow for 20Fr calibration, we prefer a 1-stage dorsal inlay buccal mucosa graft urethroplasty. If the stricture does not allow for 20Fr calibration, we perform a 2-stage buccal mucosa graft urethroplasty.

We have also published our outcomes on the use of single stage and 2-stage buccal mucosa graft urethroplasty and perineal urethrostomy for longer LSUSD.[44] A 2-stage repair is only performed if the urethral plate is obliterated (<5 mm) or at the discretion of the surgeon. Our preferred single stage technique is the 1-sided dorsal onlay approach described by Kulkarni et al (fig. 5).[45] Our preferred perineal urethrostomy technique is the inverted U-shaped scrotal flap originally described by Blandy et al (fig. 6).[46] The advantage to this particular fasciocutaneous flap perineal urethrostomy is that the urethra is not transected (leaving the blood supply to the urethra intact) and the flap can easily reach to the verumontanum if necessary (which is proximal to the extent of LSUSD). In our study success rates were 79% for 2-stage repairs, 75% for 1-stage repairs and 93% for perineal urethrostomy at 32.4 months of follow-up. Additionally, a recent multi-institutional study comparing males with anterior USD >6 cm who underwent perineal urethrostomy or substitution urethroplasty indicated that patient reported outcome measures by males who underwent perineal urethrostomy were comparable to those of long stricture anterior urethroplasty with no deleterious effect on sexual function.[47] We use these data preoperatively to counsel our patients with significant LSUSD on the surgical challenges of this disease and help them decide on the best surgical option to meet their goals. We do offer repeat urethroplasty after failed primary

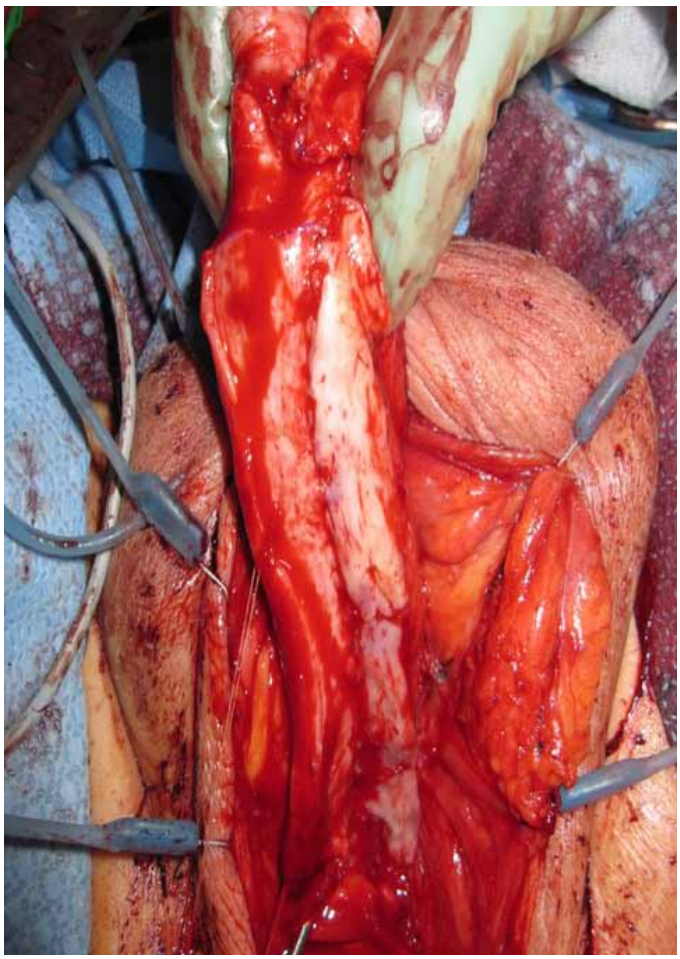

Figure 5. Kulkarni 1-sided dorsal onlay buccal graft urethroplasty dissection.

Figure 6. Patent perineal urethrostomy posteroperatively with surrounding LS skin changes.

reconstruction, although some patients do well with endoscopic balloon dilation while others elect to pursue perineal urethrostomy.

Acquired Buried Penis: **The main goal of an acquired buried penis repair operation is to achieve successful long-term penile unburying that allows for improved urinary control, genital hygiene and sexual function.** Depending on the severity of the concealed penis, multiple surgical techniques are used. If after releasing the cicatrix of scar the penile skin is found to be permanently scarred and disfigured due to LS, we excise this skin and perform split thickness skin graft coverage. Many of these patients will also have excess scrotal skin requiring complex scrotoplasty to achieve an optimal cosmetic outcome. Additionally, many if not most cases require an escutcheonectomy and in some cases a panniculectomy as well to achieve successful unburying. These surgical management techniques have been thoroughly described in the literature.[48, 49] Failure of acquired buried penis repair surgery is usually defined as the need for an additional operation for unburying purposes. Reported success rates are high but most studies are small, single center and retrospective in nature with limited follow-up.[25, 50, 51]

In 2 studies on patient reported outcomes patients who underwent acquired buried penis repair reported significant improvements in hygiene, and urinary and sexual function.[22, 52] In patients with concomitant USD the severity of acquired buried penis, location and length of the stricture, and patient bother dictate whether USD management is performed prior to acquired buried penis repair, at the time of repair or not at all. Meatal stenosis and/or fossa navicularis strictures can usually be successfully managed at the time of acquired buried penis repair with extended meatotomy or endoscopic balloon dilation. For more severe, long segment USD, urethral reconstruction can be performed several months before acquired buried penis repair.[23-25] An advantage to performing substitution urethroplasty prior to acquired buried penis repair is that the reconstruction can be performed with penile inversion while avoiding the subsequent split thick skin graft placement to the penile shaft during acquired buried penis repair. Those patients with significant USD should be counseled preoperatively that perineal urethrostomy is a viable management option as well. A subset of patients with acquired buried penis will have non-obliterative USD present with minimal to no LUTS and adequate bladder emptying. In this situation we proceed with acquired buried penis repair without USD management unless 12Fr urethral catheter placement is not successful intraoperatively.

Female LS management. As with male genital LS, potent topical corticosteroids are considered first line treatment for female genital LS.[4, 30] Goals of therapy are to improve genital pruritus, improve dyspareunia to allow for sexual activity, prevent tissue scarring and vaginal stenosis, and potentially prevent malignant transformation. Topical calcineurin inhibitors have been described for vulvar LS but there is a theoretical concern that these immunosuppressive agents increase the risk of malignant transformation and, therefore, they should be considered a second line topical therapy. Other topical treatments such as tretinoin, testosterone and estrogen have been previously attempted but evidence is lacking. However, in the postmenopausal state topical estrogens can be used as adjunct therapy for more generalized atrophic vaginitis.[30] Historically, vulvectomy was performed for vulvar LS but this has been shown to be an ineffective treatment and is now strongly contraindicated. However, simple adhesiolysis procedures can be performed for symptom relief in the setting of concurrent topical corticosteroid use to help prevent future re-fusion. Laser and phototherapy have been described but should not be considered standard of care therapy at this time.

CONCLUSION

Genital LS and LSUSD have a wide spectrum of clinical presentation with varying degrees of disease severity. They can be challenging diagnoses to treat, although current medical and surgical treatments can be successful. Urologists should have a low threshold to involve reconstructive specialists due to the complex nature of surgical repair. Further research is needed to better define the exact etiology, establish specific diagnostic criteria and develop improved treatments for this challenging spectrum of disease.

DID YOU KNOW?

- Lichen sclerosus is a chronic inflammatory, scar forming dermatologic disease that predominately affects the genitalia, and can lead to a spectrum of genital skin involvement and urethral stricture disease.
- The typical dermatologic findings include white or gray discolored and atrophic appearing genital skin with evidence of tissue scarring and irritation including induration, excoriations and fissures, and tissue fusion/adhesions.
- Topical corticosteroids are considered first line management for genital lichen sclerosus. Clobetasol propionate 0.05% is the most common corticosteroid used.
- Patients with lichen sclerosus urethral stricture disease should be counseled about treatment options including intermittent catheterization with intraurethral steroids, urethral reconstruction with oral mucosa grafting and perineal urethrostomy.
- One of the most important clinical manifestations of lichen sclerosus is the potential for malignant transformation, which is reported in approximately 2% to 8% of males, for which long-term follow-up is strongly encouraged.

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Study Questions Volume 39 Lesson 14

1. A 37-year-old man has LSUSD and a retrograde urethrogram shows a panurethral stricture from the meatus to the bulbomembranous junction. He desires surgical intervention and is adamant that he wants to be able to stand to urinate. The next step is
   a. perineal urethrostomy
   b. extended meatotomy
   c. direct visual internal urethrotomy
   d. oral mucosa graft substitution urethroplasty

2. First line management of genital LS involving the glans penis should include
   a. antimicrobial therapy
   b. topical corticosteroids
   c. topical testosterone
   d. cryotherapy

3. A 42-year-old morbidly obese, uncircumcised man has gradually experienced worsening pain with erections in the last 3 months. Physical exam shows white discoloration of the prepuce and glans. The involved skin is indurated with skin fissuring present. Meatal stenosis is seen. The next step is
   a. urinary symptom based patient questionnaires
   b. urine cytology
   c. renal ultrasound
   d. cystoscopy

4. The Koebner phenomenon describes the
   a. association of Borrelia burgdorferi infection with genital LS
   b. 2-hit hypothesis for LSUSD development and progression
   c. development of skin lesions along previous sites of trauma
   d. role of a systemic pro-inflammatory state in genital LS development

5. A 74-year-old obese man with diabetes mellitus, coronary artery disease and peripheral vascular disease has genital LS involving the glans. Retrograde urethrogram reveals a stricture of the fossa navicularis urethra. He has tried topical corticosteroids to the glans but continues to struggle with bothersome weak urinary stream and incomplete emptying. He prefers to avoid surgery given his age and comorbidities. The next step is
   a. oral alpha-1 blocker
   b. oral 5-alpha reductase inhibitor
   c. topical calcineurin inhibitor
   d. intraurethral corticosteroids with intermittent catheterization

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