**Review Article**

**Review of the male genital lichen sclerosus and urethral involvement**

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**Abstract:** Lichen sclerosus (LS) previously known as balanitis xerotica obliterans, is a chronic, progressive lymphocyte mediated skin disease. It shows a predilection for the male genital area and may involve in external urinary meatus, penile urethra and even bulbar urethra causing stricture. Male genital lichen sclerosus (MGLSc) may lead to a significant impairment of urinary and sexual function; and it has also been associated with a risk of malignant transformation. The epidemiology, natural history, histological features and possible aetiology of this disease have been researched in recent years. The direct relationship between MGLSc and penile squamous cell carcinoma (SCC) remains to be established. Biopsy of the initial lesion for definitive diagnosis and long-term follow up of affected patients are well established. The aetiology of the disease is incompletely characterized to date. The goals of the treatment are to alleviate symptoms and discomfort, prevent anatomical changes such as urethral stricture and prevent malignant transformation. Topical corticosteroid and circumcision can be curative if the disease is treated early when still localized. Severe MGLSc and urethral involvement may require extensive treatment. Various surgical procedures like simple meatotomy, staged urethroplasty using oral mucosa and complicated urethral reconstruction have been widely used depending on the length and severity of urethral stricture. Biopsy and long-term surveillance are recommended. Further research is needed to improve the prevention, understanding and treatment of this challenging condition.

**Keywords:** Lichen sclerosus, balanitis xerotica obliterans, male genitalia, urethral stricture

**Introduction**

Lichen sclerosus (LS), also known as balanitis xerotica obliterans (BXO), is a chronic and progressive inflammatory skin disease of unknown origin. It may affect any cutaneous surface but shows a predilection for the genital area in both sexes. Male genital lichen sclerosus (MGLSc) may cause destructive scarring, which can lead to devastating urinary and sexual problems and a dramatic reduction in quality of life [1].

Over the years, a variety of different names have been used to describe this condition. Hallopeau clinically described the disease process for the first time in 1887 and named it *lichen plan atrophique*. In 1892, Darier described the histological features of this disease and named it *lichen plan sclérex*. The male form of BXO was first described by Stühmer in 1928 [2]. Its name was derived from 3 components: balanitis-chronic inflammation of the glans penis; xerotica-the abnormally dry appearance of the lesion; and obliterans-the association of occasional endarteritis. BXO was synonymous with LS for a long time. However, the International Society for the Study of Vulvovaginal Disease officially adopted the term LS to define this disease process in 1976 and stated that it should be used preferentially [2, 3]. In 1995, the American Academy of Dermatology recommended that the term LS be used in future reports, and the current literature suggests the use of this term instead of BXO [4, 5].

**Epidemiology**

MGLSc has been identified in patients of all ages. The exact prevalence is difficult to estimate because patients may present to various specialists [6]. However, it is likely more com-
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More common than previously reported. The prevalence was estimated 1/300 to 1/1,000 of all patients referred to a community based dermatology department. However, a more recent study reported the incidence was 1.4 per 100,000 (0.0014%) and the epidemiology may vary between countries and racial groups. It occurred more commonly in white males and was most commonly diagnosed after the third decade of life, while the incidence in Asian and Pacific Islander men was lower. Interestingly, there was a significant association between region and MGLSc diagnosis with the highest incidence in the Pacific northwestern United States [7]. Kizer reported that the incidence in black and Hispanic patients was twice than in white patients [8].

Clinical presentation

The disease has been described as an insidious condition with slow progression. It usually initially affects the glans and foreskin [7]. In the early stage, the skin shows clinically nonspecific findings of erythema with hypopigmentation, often in association with pain pruritus and a burning or pricking sensation. These symptoms generally occur as a result of irritation of the nerve endings of the skin or the stretching of the skin due to edema and a reduction in its elasticity. As the disease progresses, the lesion on the glans can resemble those found in erythroplasia of Queyrat, lichen planus, leukoplakia or scleroderma. A combination of white plaques and normal red tissue may give a mosaic appearance to the lesion. Recurrent ulcers with purulent secretions appear on the prepuce and frenulum, and then the prepuce fuses with the glans, accompanied by areas of pallor, atrophy and sclerotic plaques, causing the foreskin to become nonretractile (Figure 1). In the end-stage, the diseased skin may become inelastic and foreskin fixed in retraction. The complications have a significant impact on male sexual health [9].

Some centers specialized in urethral reconstructive surgery have reported an increasing urethral involvement in MGLSc [1]. The involvement of the urethra and urethral stricture usually begins at the meatus, and mucosal involvement and spongiosis can spread proximally as far back as the posterior urethra, leading to obstructive urinary symptoms in long-standing disease [3]. A retrospective study reviewed the records of 522 MGLSc patients, showing urethral involvement in 20% and involvement of the meatus in 4% [10]. Barbagli reported 106 patients who underwent urethroplasty for anterior urethral strictures and 31 (29%) who received a specific pathological diagnosis of MGLSc [11]. A study described 215 patients who underwent surgery for histologically proven MGLSc involving the foreskin and/or anterior urethra and 135 (62.8%) who had panurethral strictures, in whom the navicularis and penile urethral mucosa showed the same histological features as MGLSc in the penile skin [1]. The reason for the involvement of the urethra remains unknown. The embryology of the glans may explain the involvement of the external urinary meatus and navicularis tract. The development of the glanular urethra involves the fusion of the preputial folds to the genitals folds, and because of its embryologic origin, skin diseases may involve the glanular urethral mucosa [12].

MGLSc urethral involvement and its proximal extent have been well demarcated [4]. Barbagli reported the involvement of MGLSc through the navicularis and penile urethra but not in the bulbar urethra [13]. Peterson found a definitive cut-off point for the spread of the disease in the proximal bulbar urethra and did not detect the progression of the stricture into the prostatic urethra [14]. The reason for the presence of a proximal urethral stricture in some patients may be trauma from repeated dilatations or instrumentation [12]. The glans penis differs markedly from the penile and bulbar urethra in total collagen content and glycosaminoglycans composition, which are components of the
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Figure 2. Retrograde (A) and voiding urethrography (B): irregular narrow contour of nearly the entire anterior urethra, the periurethral and bulbous glands can be clearly seen with contrast medium.

Figure 3. Histological appearance of lichen sclerosus: A band-like infiltrate of lymphocytes and plasma cells in the basal epidermis, hyperorthokeratotic squamous epithelium with vacuolar degeneration of basal cells, hyalinization of collagen in the upper dermis and hyperkeratosis across the epithelium (haematoxylin and eosin stain; original magnification ×100).

extracellular matrix, with a higher concentration of hyaluronan and a lower concentration of heparan sulphate. These differences suggest that different segmental responses to injury may occur in MGLSc urethral involvement [15]. MGLSc urethral involvement and stricture in patients result in urethritis, voiding difficulties, urinary retention and potentially effects on the upper tracts. The involved urethral mucosa often looks pale and shaggy with occasional focal fissuring or ulceration on cystourethroscopy. The examinations of cystourethroscopy and urethrography (Figure 2) were recommended to establish a definitive diagnosis and to determine the proximal extent of the disease [10].

Histology

The diagnosis of MGLSc should be made on the bases of clinical and biopsy findings (Figure 3). During the early stage of the disease, specific histological features showed a moderately heavy lymphocytic infiltrate develops in the basal epidermis and superficial dermis, accompanied by basal vacuolar change in the epidermis. In cases with pronounced vacuolar change, the epidermis may detach from the dermis with hemorrhagic bullae may form, and the epidermis may become atrophic with various degrees of hyperkeratosis. As the lesion develops, a loss of elastic fibres occurs in the papillary dermis, and the dermal inflammatory infiltrate is displaced downwards due to subepidermal oedema [5, 9]. The classic lesion is characterized as hyperkeratosis of the epithelium, hydropic degeneration of the basal cells, sclerosus of the subepithelial collagen, dermal lymphocytic infiltration and atrophic epidermis with the loss of rete pegs and homogenization of the collagen in the upper third of the dermis [4, 15].

LS and Penile squamous cell carcinoma (SCC)

SCC was associated with a number of established risk factors and associated diseases or
conditions, such as phimosis, human papillomavirus (HPV) infection, poor hygiene and smoking. Recent research suggested MGLSc was the most important non-HPV-related condition associated with SCC [16]. The two diseases are well-known to be more common in uncircumcised men, and the relationship between them has been clarified recently [17]. As MGLSc and SCC the risk has been estimated at between 2% and 12.5% [10]. Another recent study showed the risk of malignant transformation of MGLSc is 4-8% [18]. There is a significant proportion of patients with penile malignancy have a histological diagnosis of MGLSc, 155 penile carcinoma patients found evidence of MGLSc in 28% [19]. Barbagli studied 130 patients with MGLSc, revealed 11 men (8.4%) with premalignant or malignant features, the time interval between MGLSc and the development of SCC was 14-30 years [20]. Powell found histological or clinical evidence of MGLSc in 11 of 20 patients with SCC of the penis and it appeared to be a definite association between penile carcinoma and MGLSc [17]. The disease may play a precancerous role in the development of SCC [21]. However, other studies considered the role of the disease as a premalignant lesion remains unclear and its association with the risk for recurrent SCC needs to be determined [16, 19].

Histology is essential to confirm the clinical findings of this disease and to provide evidence that no premalignant or malignant changes have occurred [12]. It is recommend not only routine histological examination of all circumcision specimens, but also a regular follow-up for MGLSc [10, 17, 19]. More long-term prospective studies are recommended to determine the real risk of malignant transformation of MGLSc.

Aetiology

Because of the frequent failure to recognize the condition, the fragmentation of care in various specialties, and the use of different names by different specialists for the same entity, the aetiology of MGLSc is incompletely characterized [2], the true risk factors for the disease have not been determined to date, but it is most probably multifactorial and a variety of theories have been proposed.

One of the most accepted theories is immune dysregulation [22]. Specific antibodies have been found in patients with MGLSc, and an increased incidence of other autoimmune conditions such as thyroid disease, diabetes, vitiligo, alopecia areata, pernicious anemia, scleroderma and rheumatoid arthritis have been reported in MGLSc [10, 23]. Some organ-specific antibodies such as anti-thyroid, gastric (parietal-cell) tissue, intrinsic factor, antinuclear and anti-smooth muscle autoantibodies have also been found in MGLSc [24]. However, the different comment that the association with these autoimmune diseases is so infrequent that testing for autoimmune diseases is not indicated in MGLSc.

There may be a genetic basis in some cases of MGLSc. The human leukocyte antigen (HLA) complex is known to determine an individual’s susceptibility to inflammatory diseases. It is reported HLA-DR11, HLA-DR12 and HLA-DQ7 have increased frequencies in MGLSc [25]. Filaggrin is a key protein that facilitates terminal differentiation of the epidermis and formation of the epithelial barrier, barrier defect due to filaggrin mutations might contribute to the susceptibility of genital epithelium to urinary irritation in MGLSc [26]. However, the well defined genetic association has not been identified in the majority of cases of MGLSc to date.

Several infective agents may link to MGLSc, including pleiomorphic and variably acid-fast bacilli and the spirochete Borrelia burgdorferi [2, 27]. HPV has been detected in MGLSc tissue by polymerase chain reaction [28]. A variety of HPV sub-types such as HPV 16, 18, 33 and 51 have been reported in MGLSc [29], while another recent study showed that there was no correlation between the two conditions [30]. The possible association of hepatitis C with MGLSc has also been investigated [31, 32]. Epstein-Barr virus (EBV) DNA has been found in 26.5% of 34 vulvar biopsies with female LS patients, but the role in MGLSc has not known [33].

The Koebner phenomenon can trigger MGLSc at sites of trauma, old scars, those prone to constant friction, and those that have been subjected to sunburn or radiation treatment [23, 34].

MGLSc is definitely a disease of the uncircumcised male and it is exceedingly rare in the male circumcised at birth indicating that the foreskin must play an obligate role in the pathogenesis.
of the disease [30]. A recent study has shown that 91-100% MGLSc have dribbling compared to 14% controls. It has been proposed post-micturition dribbling or microincontinence plays a central role in the etiopathogenesis of MGLSc [35].

A recent study suggested that there might be a metabolic or lifestyle component in the etiology of MGLSc. Increased rates of elevated body mass index, diabetes mellitus, coronary artery disease and smoking were observed in MGLSc [36, 37]. The use of drugs like beta-blockers and ACE inhibitors has shown an inverse relationship to the presence of vulval LS [38]. Sex hormones may contribute to the development of female LS, but they have not been demonstrated to influence the disease process in males to date [39].

Management

MGLSc can be clinically controlled but hard to cure. The goals for treating the disease are alleviating symptoms and discomforts and preventing anatomical changes, such as urethral stricture and malignant transformation [2, 40]. It is imperative to use simple and easily applicable criteria in its management.

Medical treatment

Topical corticosteroid preparations are the main stay for the treatment for MGLSc. They are known for their potential to inhibit chronic inflammatory processes and may be helpful in reducing initial symptoms and slowing disease progression [9, 41]. A potent topical corticosteroid used under supervision for a finite course is effective, Betamethasone dipropionate 0.05% or clobetasol propionate 0.05% cream or ointment is used as suitable potent topical corticosteroids [5]. The use of a topical steroid treatment and reassurance of the long-term safety of topical steroids usually helps to achieve a beneficial outcome [42]. There is no universally accepted treatment guideline regarding the type of topical steroid to use or the treatment duration. Clobetasol propionate 0.05% administered twice daily for 2 to 3 months with a gradual reduction in the dose has been used with success [10].

The topical calcineurin inhibitors pimecrolimus and tacrolimus also have been used in MGLSc with success [42]. The topical 0.1% tacrolimus ointment is safe and tolerable for the treatment of established MGLSc and provides effective control of the disease [43]. This ointment is also a safe and tolerable adjuvant option after surgery for MGLSc, particularly if there is a risk of a complicated outcome due to urethral involvement [44, 45]. Another report indicated topical calcineurin inhibitors should not be used because of a theoretical synergistic risk of SCC [46]. Long-term safety of calcineurin inhibitors has not been established and it has been advised not be used as first-line therapy [42]. Systemic oral corticosteroids have no role in management of MGLSc and should be avoided [5].

Surgical treatment

Circumcision

Surgical treatment of MGLSc often involves circumcision for confirmation of pathology and to alleviate symptoms and offer cure in many cases. Circumcision may have an important role in the management of early disease because it may allow mildly diseased tissue of the glans to revert to normal within months [9]. Depasquale has reported a large case series of 287 patients with MGLSc that 92% limited to the glans and foreskin are successfully treated with circumcision alone [10]. It should be noted that the diseased glans will be assisted by circumcision, possibly due to elimination of the moisture rich environment that can harbor precipitants [47].

Meatoplasty

Urethral involvement is variable and may involve the meatus, navicular fossa and even the penile urethra. Meatal stricture can be treated with ventral meatotomy or dorsal V-meatoplasty. Extended meatoplasty (EM) with the creation of a hypospadiac meatus may be the initial surgical treatment for some patients and it has been reported to be successful in 14 of 16 men (87%) with complex or reoperative strictures [48]. A new meatoplasty series described by Steffens includes both ventral and dorsal meatotomy procedures, which allows for the creation of a wide opening that is less vulnerable to restenosis while retaining the meatus at the tip of the penis. This procedure produces a good cosmetic result, and
nearly all of the patients who have received it are pleased with the results [49].

Glans resurfacing

Severe MGLSc may require extensive surgery involving either glans resurfacing with grafting or complete degloving with or without split skin grafting depending on any previous circumcision [50, 51]. To control the disease, maintain the function (voiding and intercourse) and cosmesis need to be carefully balanced before treatment. Glans resurfacing has become popular due to the high graft take rates and also because reasonable cosmesis can be obtained [10].

Staged urethroplasty and reconstruction

The treatment of the urethral complications of MGLSc is known to be problematic. Many studies have advised that the disease be addressed in a stepwise manner and that medical therapy and/or minimally invasive surgical therapy be carefully considered, while understanding that many patients may eventually require more extensive or complex reconstruction [4]. The main goal of urethral reconstruction is to provide all patients not only with satisfactory disease treatment but also with a satisfactory self-image of body integrity [1].

It has been suggested that it may be reasonable to use flaps or onlay graft repair to manage short strictures early in the reconstructive process, saving the maximum amount of preferred tissue for complex repairs at a later date [4]. However, most studies have indicated that nongenital skin should be used because MGLSc is a skin disease, and any skin used for repair could be already diseased or may become diseased [52]. Thus, genital skin is not recommended in the surgical management of the disease. In a report of 28 MGLSc patients, 12 were treated with pedicled penile skin flap urethroplasty, and the other 16 were treated by excision of the diseased segment and two-stage free graft urethroplasty using nongenital skin. All 12 urethroplasty procedures using the genital skin flaps failed, while only 1 of the 16 patients who received a nongenital skin graft showed the failure at a follow-up [3]. Another report described a stricture recurrence rate of 90% when genital skin is used as a graft, whereas recurrence does not occur in patients who have undergone reconstruction with buccal and/or bladder mucosa [10].

Oral mucosa graft is always used in patients with penile urethral strictures. The addition of a buccal mucosa graft has proven invaluable in the treatment of with MGLSc, providing less contracture and more reliable revascularization [53]. One-stage repair procedure has been successfully performed on patients showing slight or moderate disease without full involvement of the glans and penile skin and with a reasonably wide urethral plate. Dubey reported an 88% success rate for full-length one-stage oral mucosal graft urethroplasty for MGLSc [54]. Two-stage repair has been advised for severe patients with full involvement of the glans and penile skin and with a narrow and scarred urethral plate [1, 55]. A new technique has been reported involving the excision of the urethral plate followed by the complete opening of the glans and the grafting of the buccal mucosa (BMGs) to the tunica albuginea during the first stage and urethral tubularization during the second-stage 6 to 12 months later [56]. Lingual mucosa grafts (LMGs) have also been used as urethral grafts in urethroplasty. The tissue is identical in structure to the buccal mucosa, consisting of a thick epithelium, high content of elastic fibers, thin lamina propria, and rich vascularization [1, 57]. Xu studied the two grafts and considered 1-stage urethroplasty with single or combined LMGs or BMGs may be an effective option to treat urethral stricture associated with MGLSc [58]. Thus, one-stage or staged repairs using oral mucosa grafts are the most recommended procedures for the treatment of MGLSc urethral strictures [59].

Recently, bladder-derived acellular and collagen matrix tissue-engineered tubularized urethras have been used in patients needing complex urethral reconstruction [60]. However, more long-term studies are needed to confirm the effectiveness of the tissue-engineer material.

Perineal urethrostomy and other management options

Perineal urethrostomy may be a good option for patients with long urethral strictures, severely scarred urethral plate, previously failed repairs and comorbidities, and those who are not willing or are medically unfit to undergo urethral reconstruction [61].
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Cryotherapy, ultraviolet phototherapy, carbon dioxide laser, pulse dye laser and subcutaneous injection of absolute alcohol have been attempted for MGLSc treatment [9]. Most of these are not ongoing investigations and have no studies with large numbers to support their use. Thus, further research into other therapies is needed.

Conclusions

MGLSc is a chronic, progressive and inflammatory skin condition that can occur in individuals of any age. It shows a predilection for the genital area and may involve in anterior urethra causing stricture. Topical steroids may help to delay the progression of this disorder. Circumcision may have an important role in the management of the disease. Severe MGLSc may require extensive therapy, various surgical procedures and complicated urethral reconstructions have been widely used. The association between MGLSc and penile carcinoma remains to further research. The patients need extensive counseling and education to fully grasp the nature of the disease process, and require long-term follow-up.

Disclosure of conflict of interest

None.

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