

The Aetiopathogenesis of Male Genital Lichen Sclerosus (MGLSc)

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Abstract:

Male genital lichen sclerosus (MGLSc) is a skin disease that causes significant male sexual dyspareunia and urological morbidity. It can also be complicated by squamous cell carcinoma of the penis. The aetiopathogenesis of MGLSc has been subject to much conjecture and genetic, autoimmune and infective [such as human papillomavirus (HPV) hepatitis C (HCV) and *Borrelia*] factors have been proposed. However, there is a compelling argument that chronic, occluded, exposure of susceptible epithelium to urine is central to the aetiopathogenesis of MGLSc.

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Introduction

Male genital lichen sclerosus (MGLSc) is an acquired, chronic, inflammatory and fibrosing cutaneous disease of unknown aetiology. It causes acute and chronic balanoposthitis and scarring that can result in significant sexual and urinary dysfunction as well as conferring a risk of squamous carcinoma of the penis.^{1,2}

The incidence and prevalence are unknown, perhaps partly because of significant under-reporting. The epidemiology will necessarily vary between countries and racial groups because MGLSc is essentially a disease of the uncircumcised; indeed it is a common reason for circumcision in boyhood and adulthood and there is a bimodal age incidence with peaks in young boys and in adult men, late in the fourth decade.³⁻⁷

The presentation of MGLSc of the penis varies. It may be asymptomatic. Some patients describe spontaneous itching, burning, bleeding, tearing, splitting, or hemorrhagic blisters or urinary problems such as dysuria and narrowing of the urinary stream, or anatomical changes of the genitalia. The main presentation in men is of dyspareunia or sexual dysfunction.⁴ Other presentations are non-retractile foreskin (phimosis), foreskin fixed in retraction (paraphimosis), urethral stricture, urinary retention and renal failure. Some cases are diagnosed at the presentation of frank squamous carcinoma. Classical signs of MGLSc include atrophic ivory-white patches (leukoderma) or plaques, hypertrophic, slightly scaly lichenoid patches or plaques with telangiectasia. A constrictive lichenoid posthitis is commonly seen associated with a fibrotic preputial band causing "waisting" of the penile shaft. Urethral involvement may be subtle with meatal "pin hole" narrowing, but may be more common and extensive. The clinical presentation can be subtle or florid with adhesions, obliteration of anatomical definition and effacement of architectural structures such as the frenulum and coronal sulcus.^{1,2,4} MGLSc may, very rarely, cause perianal disease in males.^{1,2}

The aetiopathogenesis of MGLSc is unknown.

Prior postulated pathogenic factors in GLSc include genetic and environmental influences and infections such as Borreliosis, human papillomavirus (HPV) and hepatitis C (HCV).

Genetic factors

Familial lichen sclerosus (LSc) has been reported in identical and non-identical twins, sisters, mothers and daughters. However there is little evidence of a familial predisposition to LSc in boys.⁸ The human leukocyte antigen (HLA) complex is known to determine an individual's susceptibility to inflammatory diseases by influencing both cellular and humoral immunity. Most of this work has been done in women. HLA-DQ3, -DQ7, -DRB1*12 and the haplotypes HLA-DRB1*12, -DQB1*03:01/04/09/010 were found to increase susceptibility to female genital (FG)LSc, whereas HLA-DR17, -DRB1*03:01/04 and the haplotypes HLA-DRB1*03, -DQB1*02, -DRB1*03:01, DQB1*02:01/02/03 appear to protect against (FG)LSc.⁹⁻¹¹ Increased frequencies of HLA-DR11, -DR12 and DQ7 have been reported in a study of 58 males with MGLSc.¹²

Autoimmunity

A personal and/or family history of autoimmune disease has been shown to be associated with LSc. Organ specific antibodies such as those directed against thyroid and gastric (parietal-cell) tissue have been found in patients with LSc. Autoimmune conditions such as diabetes, vitiligo and alopecia have been reported in patients with LSc.^{10,13,14} Autoantibodies to extracellular matrix protein (ECM1) have been found in FGLSc and MGLSc but may be an epiphenomenon.^{15,16} LSc shares some clinical and histopathological features with lipoid proteinosis, a rare autosomal recessive genodermatosis associated with pathogenic loss-of-function mutations in the extracellular matrix protein 1 (ECM1) gene¹⁷, so it has been hypothesized that ECM1 autoimmunity might contribute to the aetiopathogenesis of LSc.¹⁶

Infection

Several infective agents have been linked with LSc. These include acid-fast bacilli and spirochetes.¹⁸⁻²⁰ Acrodermatitis chronica

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atrophicans caused by *Borrelia burgdorferi* has some clinical and histological analogy with LSc. Such an association has been disproven by previous work of ours.²¹ HPV infection has been implicated as a causative agent. A variety of HPV sub-types such as HPV 16, 18, 33 and 51 have been reported in MGLSc.²² However, we have shown a lack of clinical correlation with HPV and an HPV-unrelated transcriptosome,^{4,23} endorsing the view that HPV might be an innocent bystander.²⁴ A link with HCV has been suggested by case reports but a recent study by us shows that HCV infection is highly unlikely to play a pathogenic role in MGLSc.²⁵⁻²⁷

Environmental factors

LSc manifests the Koebner phenomenon. It can arise at the sites of trauma, in old scars (e.g. after vulvectomy and circumcision), on skin grafts, at sites prone to constant friction, and after sunburn or radiation treatment.²⁸⁻³²

Exposure to urine

MGLSc is unequivocally a disease of the uncircumcised male.⁴ MGLSc is exceedingly rare in the male circumcised at birth indicative the foreskin must play a role in the aetiopathogenesis of MGLSc. However, MGLSc does occur in the circumcised male: with hypospadias, with genital jewellery (piercing) and after surgery, trauma and instrumentation. It does recur in grafts especially skin grafts more than mucosal grafts.^{4, 33-35} An idea that has emerged is that naviculomeatal valve dysfunction (NMVD) and urinary dribbling are central to the aetiopathogenesis.³⁶⁻³⁸ Many men presenting with MGLSc confess to dribbling post-micturition³⁹ and are often found to have an abnormal urethral meatus or navicular fossa putatively affecting the performance of the naviculomeatal apparatus as a low pressure valve. The embryology of the distal urethral, navicular fossa and meatus is complicated and a meticulous physical assessment reveals subtle variation of naviculomeatal valve structure and function between individuals. In the circumcised male, a tiny drop of urine appearing at the meatus post-micturition will have negligible contact with a keratinized glans before absorbed by

undergarments. In an uncircumcised male, with a similarly dysfunctional terminal urethral apparatus, the situation is very different. A drop of urine emanating from the tip of prepuce, glans and distal shaft of the penis, will spread widely between opposed foreskin and penis when the foreskin is covered: occlusion and the phenomenon of koebnerization precipitate inflammation; inflammation progresses to sclerosis.^{4,37,40-43} Whether MGLSc is a non-specific pathological response to urinary exposure or there is some specific mechanism or culpable constituent of urine remains unknown. Our magnetic resonance spectroscopy work suggested that there is not one single indictable component of urine.⁴⁰

The role of chronic exposure of urine to susceptible epithelium as the predominant causative agent in MGLSc is also suggested by the striking differences in the anatomical distribution of GLSc observed between men and women. In women, LSc affects the vulva and anus in a “figure of eight” configuration mirroring the areas of genital skin that might come into contact with urine.² In men, dribbled urine, consequent upon post micturition microincontinence, is likely to pool and become occluded between the inner prepuce and distal penis/glans, affecting the frenulum, perimeatal glans and visceral prepuce. In men, GLSc virtually never affects the perianal area.^{2,44} In striking contradistinction to women, the male perineum is never chronically exposed to urinary irritation. MGLSc often involves the urethra in men but there is urethral involvement in women is not recognised.

Although the definition of mucosa is controversial, the proximal penile urethra indubitably possesses a true mucosa, while the circumcised glans certainly does not; the uncircumcised glans and inner visceral prepuce possibly does or does not, and the outer parietal prepuce certainly does not. There are transition zones between true urothelium and true skin. Just as there is a wide variation of size and shape of the navicular fossa, there is probably variability in the site of the epithelial

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transition zone, the degree of keratinization of the glans, the length and, thus the surface area of foreskin, and the disposition of adnexa. Perhaps urethral LSc eventuates because the transition to stratified keratinizing squamous epithelium occurs and/or urethral mucus glans are lost, too proximally, thus rendering the epithelium focally susceptible to the pernicious irritant effects of the urine.

The association of GLSc and SCC is widely recognized and the risk has been estimated at between 2% and 9.3%.^{8,45-47} MGLSc is also considered one of the two pathways for the development of penile cancer, the other being via HPV infection.^{2,21,48}

Diagnosis and Treatment

The majority of cases of MGLSc can be diagnosed clinically. If there is clinical doubt, a biopsy should be performed. A biopsy is useful to exclude neoplastic changes and differentiate LSc from erosive lichen planus, scarring cicatricial pemphigoid and lichen simplex.^{1,2} The histology of LSc is characterized by flattening of the epidermis with variable hyperkeratosis, hydropic degeneration of basal cells and an inflammatory cell dermal infiltrate. However, histology of MGLSc may be non-specific, depending on time, site and severity.⁴⁹

The goals of treatment are the reduction and abolition of sexual dysfunction, urinary dysfunction and the risk of cancer. Our understanding of the role of occlusional contact with urine due to NMVD in the pathogenesis is fundamental to the effective management and thus the prognosis of MGLSc.

Treatment protocols in GLSc are well established.⁴⁹ Our patients are treated with soap substitution, barrier preparations and ultrapotent topical steroid. We also recommend that pubic hairs be trimmed. This is to avoid hair trapping between the foreskin and the glans penis and hence minimise irritation, abrasion and consequent inflammation. If maximal conventional medical treatment is not possible or fails then circumcision is offered. Removal of the foreskin alters the local environment of glans penis: it removes the occlusive and koebnerising effects of the foreskin

and hence mitigates the consequences of urinary dribbling due to NMVD. Using this approach, our data have shown that most men are either cured by topical treatment with ultrapotent steroid (50-60%) or by circumcision (>75%).⁴ Topical calcineurin inhibitors should not be used in MGLSc because of a synergistic risk of SCC.^{4,37,38,41}

In conclusion, MGLSc is a chronic, inflammatory, scarring skin disease responsible for significant sexual and urological dysfunction. Additionally there is the risk of mutilation and death from the treatment or consequences of penis cancer. The aetiology of MGLSc is now much clearer. It is not primarily an autoimmune condition. It is likely that an interaction between the irritant effects of urine and other pathogenic factors, such as chronicity, occlusion and an as yet undetermined differential epithelial susceptibility, or reaction, to injury, are necessary for the development of GLSc. A better understanding of the aetiopathogenesis of MGLSc facilitates the treatment of MGLSc with the aim of minimizing sexual and urinary dysfunction, mitigating or abolishing the risk of penile cancer and preserving the foreskin, when possible.

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