Original Article

Prevalence and sequelae of penile lichen sclerosus in males presenting for circumcision in regional Australia: a multicentre retrospective cohort study

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Background: Lichen sclerosus (LS) in men commonly involves the external genitalia, with up to 20% of these patients developing urethral stricture disease, and a small group developing malignant transformation to penile squamous cell carcinoma (SCC). The objective of this study was to determine the prevalence of LS and its sequelae in males presenting for circumcision.

Methods: A multicentre retrospective cohort study was conducted at 8 hospitals within 3 Australian regional centres. We identified males who underwent circumcision between January 2004 and November 2018 and obtained histological and clinical data. Histopathological confirmation of LS was the primary outcome. Development of urethral stricture disease and penile cancer were secondary outcomes.

Results: Six hundred and eleven patients underwent circumcision, of which 313 (51.2%) had a specimen sent for histology. Of these, 199 (63.6%) had confirmed LS where the median age at diagnosis was 65 years [interquartile range (IQR), 40–77]. Even if the remainder of unsent specimens were free of LS, the prevalence would still be 32.6%. Amongst the patients with LS, 44 (22.1%) developed urethral strictures, 1 penile SCC (0.5%), and 1 penile intraepithelial neoplasia (0.5%).

Conclusions: The prevalence of LS in patients undergoing circumcision where the foreskin was sent for histopathological review was 63.6%. In those with LS, the prevalence of urethral stricture disease was 22.1%.

Keywords: Lichen sclerosus (LS); prevalence; balanitis xerotica obliterans; circumcision; urethra

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Introduction

Lichen sclerosus (LS) is a chronic, progressive, sclerosing, inflammatory dermatosis (1). It was previously referred to as balanitis xerotica obliterans. LS is now the preferred terminology since the disease can also affect anogenital and extragenital sites, in both men and women (2). The precise aetiology remains contentious, however, multiple contributory factors are thought to play a role, including genetic predisposition, autoimmune disease, infection and local factors such as prior trauma or chronic irritation (3).

LS in men most commonly involves the glans penis and prepuce (4). Scrotal LS is less common and perianal

Figure 1 Penile lichen sclerosus recurrence involving the glans penis and urethral meatus.

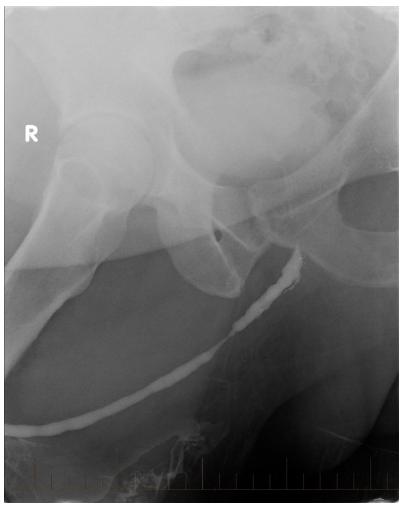

Figure 2 Pan-urethral stricture with near obliterative bulbar region in a patient with lichen sclerosus.

involvement in men is rare (1). Clinically, LS can manifest as areas of abnormal skin greying, whitening, reddening, induration, plaque formation and/or fissuring (see *Figure 1*). This can lead to phimosis, paraphimosis, painful erections, voiding symptoms and/or urinary retention. Histologically with standard Hematoxylin and eosin staining, LS is characterised in the early phase by moderately heavy lymphocytic infiltrate in the basal epidermis with associated basal vacuolar change, and similar infiltrate in the superficial dermis (1). Further progression is characterised by epidermal atrophy, surface hyperkeratosis, thickened basement membrane, broad underlying zone of sub-epidermal oedema with homogenisation of collagen, subsequent sclerosis and minimal inflammatory infiltrate deep to dermal fibrosis (1).

LS can extend to involve the urethral meatus and urethra itself, with up to 20% of patients experiencing urethral strictures (5) (see *Figure 2*). These are typically distal, but in severe cases may involve the entire urethra (6). It has been postulated that obstruction of urine at the level of the glans penis leads to extravasation of urine into the glands of Littre, with subsequent inflammation and spongiofibrosis, resulting in urethral structuring (6,7).

There is also a 0.00–8.40% risk of malignant transformation (8,9), most commonly penile squamous cell carcinoma (SCC). The process by which LS leads to penile SCC is not entirely understood, but factors thought to play a role include various dermatoses, carcinoma in situ, HPV infection, and phimosis and smegma retention in uncircumcised males (10). Despite a link with penile cancer, long-term surveillance of patients with LS is not routine.

Treatment of LS limited to foreskin with circumcision is often curative. In a retrospective study of 287 patients with BXO treated with circumcision alone and up to 14 years of follow-up, 92% did not require any further intervention and had alleviation of their symptoms (5). Even disease extending to the glans may normalise following circumcision (4). Medical management of mild-moderate cases of LS can be attempted with corticosteroids applied topically or an intralesional injection (5), and similarly these treatments may also be used as an adjunct or following recurrence after surgical treatment (1).

In patients with more extensive involvement of the glans, urethra or surrounding tissue, other surgical options may need to be considered. Urethrotomy, meatotomy, or urethral dilatation were traditionally used, though high recurrence rates has resulted in a trend towards reconstruction, including glans resurfacing, urethroplasty or even perineal urethrostomy. In these cases, LS may recur despite treatment. Even after urethroplasty, LS-associated strictures have high recurrence rates (4).

The prevalence of penile LS is not well established. A prospective study with random genital biopsy cannot be ethically justified. Therefore, the objective of this retrospective study is to determine the prevalence of LS and its sequelae in patients who underwent circumcision where a specimen was submitted for histopathological review. We present the following article in accordance with

Table 1 Histological diagnosis in patients presenting for circumcision

Histology n=313/611	Frequency	Percentage
Lichen sclerosus	199	63.6%
Acute/chronic inflammation	61	19.5%
Lichen planus	6	1.9%
Zoon's balanitis	5	1.6%
No pathology	36	11.5%
Other (hypertrophic scar, superficial fungal infection, benign keratosis, epidermal cyst)	6	1.9%
Total	313	100%

the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-22-29/rc).

Methods

A multicentre retrospective cohort study was performed at 8 hospitals within 3 major Australian regional centres. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Darling Downs Hospital and Health Services Human Research Ethics Committee (reference number: HREC/17/QTDD/56) and individual consent for this retrospective analysis was waived. All patients who underwent circumcision at the Toowoomba Hospital, St Andrew's Toowoomba Hospital, St Vincent's Private Hospital Toowoomba, Port Macquarie Base Hospital, Port Macquarie Private Hospital, Wauchope District Memorial Hospital, Kempsey District Hospital, and Mater Mackay Hospital, between January 2004 and November 2018, were included in this study. Patients with no histology or unavailable medical records were excluded. There was no pre-determined sample size. Our intent in utilising data from regional centres was to more accurately capture subsequent stricture or cancer complications, as patients are more limited to local follow-up.

The histology of circumcision specimens and patient medical records were examined. The primary outcome was histological confirmation of LS. Secondary outcomes included development of urethral strictures and penile cancer, the treatment of these LS sequelae, as well as alternative histological diagnoses, during the same time period.

Statistical analysis

The following data was collected: age at circumcision, date of circumcision, location of procedure, histopathology diagnoses, urethral strictures and treatments, and penile cancer and treatments. We reported the data using descriptive statistics and calculated the median patient age with interquartile range, and prevalence of each of the histological diagnoses and LS sequalae.

Results

We identified 611 patients who underwent circumcision and had follow-up during a 14-year study period, with a median age of 31 years [interquartile range (IQR), 9–68]. Of these, 313 patients had a specimen sent for histology (51.2%).

Rates of pathology sent for Toowoomba Hospital was 24% (40/164), St Andrew's and St Vincent's Private Hospital Toowoomba was 100% (150/150), Mater Mackay Hospital was 100% (19/19), Port Macquarie Base Hospital was 31.6% (43/136), Port Macquarie Private Hospital was 39.7% (50/126), Wauchope District Memorial Hospital was 71.4% (5/7) and Kempsey District Hospital was 66.7% (6/9).

Of the 313 patients who had a specimen sent for histology, 199 (63.6%) had confirmed LS, 61 (19.5%) had acute/chronic inflammation, 6 (1.9%) had lichen planus, 5 (1.6%) had Zoon's balanitis, 6 (1.9%) had other diagnoses (hypertrophic scar, superficial fungal infection, benign keratosis and epidermal cyst), and 36 (11.5%) had no pathology on histology. These findings are summarised in *Table 1*. To further break down the prevalence of LS within our study population, 60 out of 278 patients (21.6%) had LS in the Port Macquarie region, compared to the Toowoomba region with 122 out of 314 (38.9%), and the Mackay region with 17 out of 19 (89.5%).

Of the 199 patients with LS, 44 (22.1%) developed urethral strictures (refer to *Table 2*). Of these, 31 (70.5%) were located at the meatus, 4 (9.1%) involved the penile urethra, 6 (13.6%) involved the bulbar urethra, 1 (2.3%) was at the peno-bulbar junction and 2 (4.5%) were pan-urethral. In terms of management, 33 of 44 urethral stricture patients (75%) required urethral dilatation, 5 had urethrotomy (11.4%), 2 underwent meatotomy (4.5%), and 1 had buccal mucosal graft pan-urethroplasty (2.3%).

In terms of malignancy, 1 patient had penile intraepithelial neoplasia (0.5%) and was completely

Table 2 Urethral strictures in patients with histologically confirmed lichen sclerosus

Urethral stricture n=44/199	Frequency	Percentage
Meatal stenosis	31	70.5%
Penile urethral stricture	4	9.1%
Bulbar urethral stricture	6	13.6%
Peno-bulbar junction	1	2.3%
Pan-urethral stricture	2	4.5%
Total	44	100%

treated with circumcision, and 1 was diagnosed with invasive T3N0M0 penile SCC (0.5%) at three years post-circumcision and was treated with radical penectomy and perineal urethrostomy.

Patients with LS had a median age of 65 years (IQR, 40–77), compared with 22.5 years (IQR, 18–41) for patients with normal pathology.

Discussion

Of the 313 patients who underwent circumcision and had a specimen sent, 199 (63.6%) had a histological diagnosis of LS. Accounting for potential selection bias in the unlikely scenario that the remainder of unsent specimens were free of LS, the prevalence here would still be 32.6%. Reports in the literature of LS prevalence are highly variable. In adult men undergoing circumcision, the rates of histologically confirmed LS ranged from 1% to 67.4% (11-15). In mixed cohorts of adult and paediatric males, the prevalence of LS was 12.3–14.2% (16,17). In a study looking at only the paediatric population, the prevalence of LS was 34.5% (18). Even in this younger population LS is extremely common, reinforcing the importance of early recognition and management with circumcision which may prevent long-term complications. In selected cohorts with a pre-existing clinical diagnosis of LS, 65–93.5% of undergoing circumcision had confirmation of LS on histopathology (19,20).

Within the 14-year studied period, 22.1% of patients were concurrently or subsequently found to have urethral strictures, investigated as per clinician suspicion or urinary symptom profile with urethrogram or urethroscopy. This rate is comparable to other series reported within the literature, with 20% of patients with LS requiring stricture-related surgery (5). When a large portion of circumcision specimens are not sent for histopathology, patients with undiagnosed LS may not be adequately counselled and followed up regarding stricture risk. Subsequently the treatment of LS sequelae may be delayed, which can lead to increasingly invasive management for progressed disease. Patients should be fully informed of potential LS stricture sequelae, and carefully evaluated early through history, examination, symptom scores, flow rates and if necessary, retrograde urethrogram or urethroscopy. Therefore, higher referral of specimens for histopathological diagnosis may be reasonable.

It should be noted that 7 patients who developed stricture disease had isolated proximal urethral strictures. LS strictures originate distally, though may spread to become panurethral (6). Therefore, these cases may represent concomitant disease or shared underlying aetiology of stricture and LS, such as trauma or infection.

Penile cancer is uncommon with less than 1 case per 100,000 men in Europe and North America (21). However, LS is associated with malignancy in 0.00–8.40% of cases (8,9) and in patients with confirmed penile SCC, LS is histologically noted in 28–44% of cases (8). These figures are higher than those for penile cancer in the general population and so LS is an important risk factor (21). Despite the high incidence of LS in patients with penile SCC, there does not appear to be any increased rates of adverse histopathological features, including tumour grade, stage, presence of lymphovascular invasion, histological subtype, carcinoma *in situ* or nodal status (22). In our study population, despite a high prevalence of LS, only 2 cases (1.2%) of penile malignancy where identified. However, our patients underwent circumcision which is often curative for LS (5), and systematic review evidence suggests that men circumcised in childhood/adolescence have a substantially lower risk of developing invasive penile cancer (23). Furthermore, the incidence of penile SCC increase with age with a peak occurring in the sixth decade (21,24). Hence, it is possible that with further prolonged follow-up increased numbers of penile SCC may be detected in our cohort.

To assess prevalence through a wider population of all circumcision patients, the clinical indication for circumcision was not independently analysed. While circumcision is most commonly performed for religious or tribal reasons globally (25), in the practice of the surgeons who have provided the data for this study, circumcision was generally undertaken in those presenting with symptomatic penile pathology such as phimosis or penile infections. Therefore, only a small proportion of non-medical circumcisions would

have been undertaken but was not specifically analysed and is a limitation of this study.

In our study population, 48.8% did not have a specimen sent for histology, as specimens are commonly referred for pathological analysis only when there is clinical concern for significant underlying abnormality (25). This represents a key limitation in retrospective analysis, and restriction in assessing true prevalence, with further prospective study indicated to reduce selection bias.

The effectiveness, timing and duration of long-term follow-up for patients with penile LS is not well defined. Some authors suggest yearly review following treatment of LS, with history, flow rates, symptom scores and careful physical examination (4). However, it is unclear if such practice is feasible or beneficial for long-term outcomes. With limited healthcare resources, routine clinical review is unlikely to be economically justifiable, especially in regional areas. Instead, given the significance of sequelae of LS, patient counselling is critical to facilitate early patient presentation and subsequent identification of potential stricture disease or malignant transformation.

Conclusions

Our study suggests a high prevalence of LS (63.6%) in patients presenting for circumcision. In those with LS, the prevalence of urethral strictures was 22.1%. Current practices in attaining tissue diagnosis at circumcision may be insufficient, which has implications on patient counselling and early recognition of potentially serious complications.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-22-29/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-22-29/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-22-29/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Darling Downs Hospital and Health Services Human Research Ethics Committee (reference number: HREC/17/QTDD/56) and individual consent for this retrospective analysis was waived.

References

1. Clouston D, Hall A, Lawrentschuk N. Penile lichen sclerosus (balanitis xerotica obliterans). BJU Int 2011;108 Suppl 2:14-9.
2. Granieri MA, Peterson AC, Madden-Fuentes RJ. Effect of Lichen Sclerosis on Success of Urethroplasty. Urol Clin North Am 2017;44:77-86.
3. Powell JJ, Wojnarowska F. Lichen sclerosus. Lancet 1999;353:1777-83.
4. Belsante MJ, Selph JP, Peterson AC. The contemporary management of urethral strictures in men resulting from lichen sclerosus. Transl Androl Urol 2015;4:22-8.
5. Depasquale I, Park AJ, Bracka A. The treatment of balanitis xerotica obliterans. BJU Int 2000;86:459-65.
6. Mangera A, Osman N, Chapple C. Recent advances in understanding urethral lichen sclerosus. F1000Res 2016;5:eF1000 Faculty Rev-96.
7. Mangera A, Osman N, Chapple C. Evaluation and management of anterior urethral stricture disease. F1000Res 2016;5:eF1000 Faculty Rev-153.
8. Minhas S, Manseck A, Watya S, et al. Penile cancer--prevention and premalignant conditions. Urology 2010;76:S24-35.
9. Spekreijse JJ, Streng BMM, Vermeulen RFM, et al. The risk of developing squamous cell carcinoma in patients with anogenital lichen sclerosis: A systematic review.

Gynecol Oncol 2020;157:671-7.
10. Nasca MR, Innocenzi D, Micali G. Penile cancer among patients with genital lichen sclerosus. J Am Acad Dermatol 1999;41:911-4.
11. Aynaud O, Piron D, Casanova JM. Incidence of preputial lichen sclerosus in adults: histologic study of circumcision specimens. J Am Acad Dermatol 1999;41:923-6.
12. Czajkowski M, Żawrocki A, Czajkowska K, et al. Lichen Sclerosus and Phimosis - Discrepancies Between Clinical and Pathological Diagnosis and Its Consequences. Urology 2021;148:274-9.
13. Liatsikos EN, Perimenis P, Dandinis K, et al. Lichen sclerosus et atrophicus. Findings after complete circumcision. Scand J Urol Nephrol 1997;31:453-6.
14. Pearce I, Payne SR. Do men having routine circumcision need histological confirmation of the cause of their phimosis or postoperative follow-up? Ann R Coll Surg Engl 2002;84:325-7.
15. Shah VS, Jung NL, Lee DK, et al. Does Routine Pathology Analysis of Adult Circumcision Tissue Identify Penile Cancer? Urology 2015;85:1431-4.
16. Clemmensen OJ, Krogh J, Petri M. The histologic spectrum of prepuces from patients with phimosis. Am J Dermatopathol 1988;10:104-8.
17. West DS, Papalas JA, Selim MA, et al. Dermatopathology of the foreskin: an institutional experience of over 400 cases. J Cutan Pathol 2013;40:11-8.
18. Yardley IE, Cosgrove C, Lambert AW. Paediatric preputial pathology: are we circumcising enough? Ann R Coll Surg Engl 2007;89:62-5.
19. Edmonds EV, Hunt S, Hawkins D, et al. Clinical parameters in male genital lichen sclerosus: a case series of 329 patients. J Eur Acad Dermatol Venereol 2012;26:730-7.
20. Kravvas G, Shim TN, Doiron PR, et al. The diagnosis and management of male genital lichen sclerosus: a retrospective review of 301 patients. J Eur Acad Dermatol Venereol 2018;32:91-5.
21. Hakenberg OW, Compérat EM, Minhas S, et al. EAU guidelines on penile cancer: 2018 update. Arnhem, The Netherlands: EAU Guidelines Office, 2018.
22. Philippou P, Shabbir M, Ralph DJ, et al. Genital lichen sclerosus/balanitis xerotica obliterans in men with penile carcinoma: a critical analysis. BJU Int 2013;111:970-6.
23. Larke NL, Thomas SL, dos Santos Silva I, et al. Male circumcision and penile cancer: a systematic review and meta-analysis. Cancer Causes Control 2011;22:1097-110.
24. Hakenberg OW, Compérat EM, Minhas S, et al. EAU guidelines on penile cancer: 2014 update. Eur Urol 2015;67:142-50.
25. Mallon E, Hawkins D, Dinneen M, et al. Circumcision and genital dermatoses. Arch Dermatol 2000;136:350-4.

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