

CLINICAL REPORT

The Clinical Spectrum of Lichen Sclerosus in Male Patients – A Retrospective Study

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Lichen sclerosus (LS) is a chronic dermatosis mainly localised to the anogenital area. The aim of this study was to investigate the clinical features of LS in adult men. A retrospective analysis of records from 771 patients diagnosed with LS was made and a questionnaire was sent to all patients. The results showed that the clinical spectrum was wide. Itch, tenderness and pain were frequently reported and more than half of the patients reported that LS had a negative impact on their sexual health. Phimosis was common and almost 1/3 of the patients were circumcised before or during the study period. Eight cases (1%) of penile squamous cell carcinoma were recorded. This emphasises the need for follow-up of male patients with LS. Key words: lichen sclerosus; circumcision; penile cancer.

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Lichen sclerosus (LS) is a chronic, inflammatory disease with a predilection for the anogenital area. The aetiology is not clearly established, although there is a strong association with autoimmune diseases especially in women. Studies have shown an increased incidence of autoantibodies in patients with LS, e.g. autoantibodies to extracellular matrix protein 1, a specific skin protein (1). It is not yet clear if these autoantibodies play a causative role for LS or if they represent an epiphenomenon. In addition to autoimmunity, evidence suggests a genetic link and cases of familial lichen sclerosus have been published (2), as well as an association with different HLA-subtypes (3). Male genital LS is rare in circumcised individuals (4) and it has been postulated that the occlusive effect of the prepuce is contributory. Also, constant urinary contact has been proposed to be of importance in male genital LS (5).

The estimated prevalence of the disease is 1:300–1:1,000 (6) and it is primarily seen in postmenopausal women (7), but also men and children can be affected. In men, LS occurs mainly between the ages of 30 and 50 years (6, 8). One of the main signs in males is phimosis,

which can cause dyspareunia, and meatal involvement leading to dysuria can also occur.

The association between LS and squamous cell carcinoma (SCC) is confirmed and has been described chiefly in females. The risk of SCC of the vulva has been estimated to about 5% in women with LS (9), compared to a background lifetime risk of vulval SCC in the UK population of 0.3% (10). The association between LS and penile SCC is unclear. Data based on studies of biopsy material suggest that the risk of SCC in males with LS is also around 5% (11). Melanoma and basal cell carcinoma have been reported, but there appears to be no increase in frequency of these tumours in patients with LS.

This study is a retrospective analysis of charts from 771 male patients with LS. Included in the investigation is also data derived from a questionnaire sent to all included participants. The aims were to describe the clinical picture of male genital LS and its symptoms, prescribed therapies, prevalence of autoimmune diseases and number of penile cancer cases.

MATERIAL AND METHODS

The study was approved by the Ethics Committee of the Medical Faculty of the University of Göteborg, Sweden.

Clinical records

Clinical records from patients diagnosed with LS in the Departments of Dermatovenereology at Sahlgrenska University Hospital, Gothenburg and Södra Älvsborgs Hospital, Borås during the period 1997–2007 were reviewed. In total, 1,075 patients were diagnosed with LS during this period. Records were screened in order to include only patients with a valid diagnosis of LS and age ≥ 18 years. Included patients should also be able to fill out a questionnaire. Exclusions were due to the following reasons: records were not available for 156 patients, 14 patients were younger than 18 years, 34 patients were deceased, 4 patients had a secret identity, 10 patients had moved abroad without forwarding address and 1 patient did not want to take part in the investigation. In the remaining 856 records, 85 patients had a preliminary diagnosis of LS but this diagnosis was altered after biopsy and clinical re-examination. The diagnosis was in most of these cases changed into lichen ruber planus, Zoon's balanitis or unspecified balanitis. Finally, 771 patients (mean age 48.6 years; range 22–92) were included in the study and their diagnosis was based on typical histopathology (31%) or on different clinical criteria: hypopigmentation, petechiae and preputial constriction.

Cases of penile cancer

From the clinical charts, cases of penile cancer and cancer *in situ* were registered. Also, patient records were correlated to information from the Swedish Cancer Registry in order to identify malignancies. In Sweden it is compulsory to register all cases of cancer and cancer *in situ* in the Swedish Cancer Registry. The registry was founded in 1958 and covers the whole Swedish population.

Questionnaire

A preliminary version of the questionnaire was tested in 10 male patients with LS visiting the clinic. Unclear or poorly understood questions were discussed with the patients and thereafter a final version of the questionnaire was constructed. The focus of the structured questionnaire was general, with a part comprising questions about sexual function. It contained enquiries about e.g. symptoms related to LS, circumcision, number of visits to the doctor, treatments, other autoimmune diseases and impact on sexual health. It was sent to all 771 included patients during 2011, and patients not returning the questionnaire the first time received one reminder.

Statistical analysis

Statistical analyses were performed using R version 2.14.2, R Foundation for Statistical Computing, Vienna, Austria. Differences in proportions were tested using Fisher's exact test. Two-sample tests were carried out using Wilcoxon's rank sum test.

RESULTS

Clinical records

The diagnosis of LS for the 771 patients included in the study was based on the different criteria seen in Table I. Biopsies were performed in 273 patients (35%). The histology established the diagnosis of LS in 240 patients (88%). In 33 patients the histology was not definite and showed, in most cases, only chronic inflammation without distinct hyalinisation or atrophy. These patients were included in the study based on their clinical picture. A majority of the included patients (82%) came for 1–3 visits to the dermatological clinic, 14% were seen 4–6 times and 4% of the patients needed ≥ 7 visits. The mean follow-up was 1.40 years (range 0.08–10.5 years, 0.95 CI 1.24–1.56) for all patients except the ones who only came for one visit (249/771 = 32%). The localisation of LS is shown in

Table I. Inclusion criteria (n = 771)

Inclusion criteria	n (%)
Histopathology showing lichen sclerosis (LS)	240 (31)
Biopsy not performed or with inconclusive result. Clinically judged as LS according to the clinical criteria below	531 (69)
Three of the following criteria: hypopigmentation, petechiae, preputial constriction	44 (8)
Two of the above-mentioned criteria	232 (44)
One of the above-mentioned criteria	229 (43)
Diagnosed as LS by qualified clinician, without records of exact clinical picture	26 (5)

Table II. Localisation of lichen sclerosis (n = 771)

Localisation of lichen sclerosis	n (%)
Preputial engagement	299 (39)
Glans penis	89 (12)
Prepuce and glans penis	372 (48)
Penile shaft	2 (0.3)
Extragenital lichen sclerosis	5 (0.6)
Extragenital and genital lichen sclerosis	1 (0.1)
Data missing	3 (0.3)

Table II. The extragenital lesions were all localised on the trunk. Perianal involvement was not consistently looked for, but it was not noted as present in any of the clinical charts.

As first line therapy, 607 patients (78.7%) received a prescription for a potent or a very potent steroid. Three quarters of the patients (419/557) who had ever received a very potent steroid needed no other treatment. Tacrolimus was used as second line treatment in 4 patients. Patients with inactive disease only received information about the disease and were advised to be careful with soap and when needed use a local moisturiser. None of the included patients received testosterone cream or systemic treatment.

Circumcision was already performed in 15% (119/771) of the patients when they entered the study. Another 13% (104/771) were referred for circumcision during the study period and of these 2 patients came back for additional therapy with local steroid.

Cases of penile cancer

In total, 8 cases of penile cancer were found (8/771 = 1.0%, 0.95 CI 0.4–2.0%). Seven of the cases were diagnosed as SCC and one as verrucous carcinoma. One of the patients with SCC needed 2 operations due to a recurrence, and this was also the case for the patient with verrucous cancer. One of the patients with SCC had 2 tumours, diagnosed with 8 years in between. Of the 8 cases, 5 were diagnosed with LS before SCC and the mean time between the 2 diagnoses was 11 years (range 3–30). Two cases were diagnosed with SCC and LS at the same time and the last case was diagnosed with SCC 6 years before LS. Three other patients had carcinoma *in situ* of the penis; 2 of them with solitary lesions and one with multiple papules and a clinical presentation of Bowenoid papulosis. One patient was diagnosed with melanoma *in situ* of the penis. The prevalence of penile cancer in this cohort can be compared to the incidence in Sweden of 1.6–2.3 cases/100,000 men (data from the Swedish Cancer Registry).

Questionnaire

The questionnaire was returned by 456 patients (59%), mean age 50.2 (24–91 years of age). The mean age for onset of LS according to the results from the questionn-

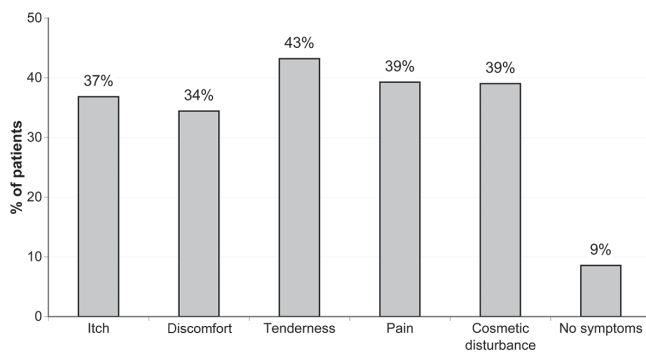


Fig. 1. Percentage of patients disclosing different symptoms ($n=456$).

aire was 36.2 years of age (range 5–77.5). The mean age for seeking medical advice was 37.8 years (5–77.5). The symptoms presented in the questionnaire are shown in Fig. 1. One third of the patients (142/456) reported that they had persistent preputial constriction. A quarter of the patients (124/456) recorded that they had ongoing or earlier meatal involvement and 39% (48/124) of these patients had at some point experienced difficulties urinating. A quarter of the patients (115/456) answered that they were cured, but 26% (30/115) of these patients noted that they had residual changes in the form of hypopigmentation.

As many as 56% (255/456) documented that LS had a negative impact on their sexual health. This figure was based on the question “Has LS affected your sexual health”? If yes (56%), also fill in the following questions: Has LS affected your sexual lust? 98 patients (21.5%) answered yes. Has LS affected your ability to have an erection? 53 patients (11.6%) answered yes. Has LS affected your ability to ejaculate? 55 patients (12.1%) answered yes. Intercourse was said to be a cause of deterioration of the disease in 26% (120/456) and 52% (238/456) experienced symptoms from their LS during intercourse.

In total, 223 patients were circumcised before or during the study period. Regarding the effect of circumcision on sexual health, 137 patients answered this question and 46% (63/137) had a better sex life, 18% (25) had a poorer sex life, while 36% (49) had not noticed any change.

Of those recording that they had used any local steroid for treatment (394/456 answered yes, 53 said no and 9 did not answer) the effect was noted as good in 30%, medium in 37% and poor in 16% (not answered by 17%).

Regarding the prevalence of autoimmune disease, 456 subjects answered this question. Six percent (27/456) registered that they had diabetes mellitus, 2% (8/456) alopecia areata, 8% (36/456) vitiligo and 2% (8/456) thyroid disease.

A statistical analysis was made of the patients not returning the questionnaire (mean age 45.7, 22–92 years of age). Non-responders were significantly younger

($p < 0.0001$) and a lower number of non-responders had taken a penile biopsy. There was no statistical difference regarding if they had undergone a circumcision or not.

DISCUSSION

In typical cases a diagnosis of LS can be made clinically and in this retrospective analysis we registered 3 distinctive signs of male LS from the clinical records: hypopigmentation, petechiae and preputial constriction. The histological picture of LS is characterised by atrophy, basal hydropic degeneration and hyalinisation in the upper dermis. All these signs may not be present and if so the histology can only support the diagnosis. In our investigation, biopsies were performed in 273 patients (35%) and the histology was classified as compatible with LS in 240 patients. The routine in our clinic is to be liberal with biopsies and it is always performed when the diagnosis is uncertain, if suspicion of dysplasia or cancer arises and in cases not responding to therapy (12).

In almost half of the 771 cases, LS affected both glans penis and the prepuce. This is in concordance with a study by Depasquale et al. (13) where the disease was found to engage the foreskin and glans penis in 57% and the meatus in only 4%. Meatal involvement was not consistently noted in our charts, but as many as 27% recorded that they had ongoing or earlier meatal involvement in the returned questionnaire. This can lead to urinary dysfunction and patients experiencing insufficient effect of local steroid treatment may need surgery. A quarter of all our patients answered that they were cured, but 26% of these patients noted that they had residual changes in the form of hypopigmentation. It has been shown that clinical signs, including pallor, can persist even after effective treatment but some researchers mean that also hypopigmentation disappears, especially if treatment is started early in the process of the disease (14). Extragenital LS was only found in 6 men (6/771) in this study, however some cases may have been overlooked since only the genital area was inspected routinely. In other studies extragenital LS has been stated to be rare in men, while it is reported to occur in ~20% of women (6). The cause of this difference between males and females is not yet known.

Not many male patients with LS report itch spontaneously, but in the questionnaire as many as 37% answered that they suffered from this symptom. Itch is more frequently reported in females with LS and it is not known why there is a gender difference (12). More than half of our patients noted that the disease had a negative impact on their sexual health, which is in congruence with a study by Edmonds et al. (5), where 55% of the male patients experienced male dyspareunia. In our study, LS affected sexual lust in 21.5% of the patients and around 10% noted that LS reduced their ability to

have an erection. Few studies addressing these issues in males are available, but in one study 27% felt that the cosmetic disturbance from LS adversely affected their libido (15). More studies focusing on this topic are required and it is important to discuss these problems when seeing patients with LS.

Clobetasol propionate is documented to be an effective and safe treatment for male genital LS (9) and data from our questionnaire showed that a majority of the patients had a medium or good effect when using a local steroid. The use of topical steroids has been proven to arrest or delay the progression of LS, as well as reversing some of the histological changes seen in the disease (16, 17). Male genital LS is seen almost exclusively in uncircumcised men and boys. It has been shown that the use of a potent topical corticosteroid often prevents circumcision (18). In our study 5.5% of the patients were circumcised already during their childhood, in 71% of these cases due to preputial constriction. Thirteen percent of our participants were referred for circumcision during the study period and only 2 of these patients came back for additional therapy with local steroid after their operation. On the other hand, in total 15% were circumcised before entering the study, and thus needed medical attention and local treatment also after this surgical procedure. In another study, as many as half of the men requiring circumcision continued to have lesions of LS after this procedure (8). Tacrolimus, a topical calcineurin inhibitor, was used in 4 patients who had inadequate effect of topical steroids. Two of these patients improved while the other 2 had no effect. In an article by Lewis & Neill (19) it is stated that "while these preparations may have a role in some patients with LS, the long-term risks need further assessment, especially in relation to the risk of malignancy".

Fifty-nine percent of the participants returned the questionnaire which can lead to a bias when interpreting the data. One can postulate that those who had experienced a good effect of the treatment and had no further problems with their LS did not send in the questionnaire. On the other hand, dissatisfied patients who felt that they had not been helped might be overrepresented in this group. A statistical analysis of the non-responders showed that they were significantly younger and also that a lower number had taken a penile biopsy. This could be because of a typical clinical picture, or because they had discrete symptoms and signs of LS. Nevertheless, there was no statistical difference regarding circumcision in the non-responders and the responders, which argues against a major difference in the clinical presentation of the disease in the 2 groups.

Another weakness with the questionnaire was that it was not possible to find a well validated questionnaire aimed at the specific patient population of males with LS and this is especially true regarding validated questions on sexual health (20).

There are limitations with a retrospective analysis and a selection bias when using a questionnaire to which not all patients answer. However, we have now randomly selected a subgroup of 100 of the included patients and seen them in our clinic during 2012. These data will be presented in a coming paper.

A strong association between LS and autoimmune disorders or autoantibodies is seen in females (21) and alopecia areata, thyroid disease and vitiligo are some of the most commonly associated diseases (6). Autoimmune diseases were not reported as frequently in our male cohort and in the questionnaire 2% of the participants recorded that they had alopecia areata, 8% vitiligo and 2% thyroid disease. However, these figures are approximate since they are self-reported. For comparison, the prevalence of alopecia areata was reported to be 2% in a population of 15,000 new outpatients seen in a dermatological clinic (22). The prevalence of vitiligo is around 1% in Europe, but ranges from 0.1% to >8% worldwide (23). Autoimmune thyroiditis is more prevalent in women than in men but in a recent report from Italy, the overall prevalence was 2.6% (24). In the British guidelines for the management of LS it is stated that screening for thyroid disease in women might be indicated, but not in men (12).

The risk of SCC is increased in female patients with LS, and it has been estimated to be about 5% (9). Several case reports have been published concerning SCC and penile LS. In a study screening pathology files for male LS and penile SCC, 5 cases of SCC were found among 86 cases of LS (5.8%) (11). The indication for taking biopsies in that study was not stated in the article, but a biopsy is usually performed when the clinical picture is not typical of LS and malignancy needs to be excluded. Thus the risk of SCC in patients with penile LS is probably lower than 5.8% in reality. In a study by Edmonds et al. (5), no cases of cancer were reported among 329 males with LS. In the present study we found that 1% (8 cases) of our participants had developed cancer during the inclusion period. So, a lower coincidence of SCC was seen in our cohort compared to reports on vulval carcinoma in women with LS. However, the number of cases was high compared to the incidence of penile cancer in the whole Swedish male population and this underlines the need for follow-up of male patients with LS. Whether effective treatment of LS can reduce the risk of cancer is not yet known (25).

In conclusion, this is one of the largest clinical reports of males with LS with a study period of 11 years. An important finding is that our patients commonly reported that LS gave them itch, tenderness or pain. LS also has a potentially negative impact on sexual health. Thus, patients with LS need long-term follow-up, as well as information about the disease, its symptoms and on the increased risk for penile cancer.

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