Dermatology Practical & Conceptual

Management of Lichen Sclerosus and Related Comorbidities at a Tertiary Referral Center: Beyond Topical Steroids

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ABSTRACT

Introduction: Lichen sclerosus (LS) is a chronic inflammatory dermatosis predominantly affecting the anogenital area, with potential systemic implications.

Objective: Our aim was to elucidate its clinical characteristics and management strategies.

Methods: We conducted a retrospective observational study on adult patients with LS referred to our center between January 2022 and December 2023.

Results: Forty-six adult subjects affected with LS were enrolled in the present study. The majority of patients presented with genital involvement, but a significant subset also exhibited extragenital LS and concomitant immune-mediated disorders. Common symptoms included itching, soreness, and dyspareunia, with characteristic skin findings of erythema and atrophy. Topical corticosteroids were the mainstay of therapy, complemented by alternative treatments in refractory cases. Alternative therapeutic approaches, such as PRP (platelet rich plasma) or ADSC (adipose-tissue derived stromal/stem cell)-based strategies, were effectively employed in refractory cases, in the absence of major adverse events.

Conclusions: Our findings underscore the importance of alternative approaches in the management of LS and highlight the need for further research to elucidate its pathogenesis and optimize therapeutic interventions.

Introduction

Lichen sclerosus (LS) is a chronic inflammatory condition that predominantly affects the genital area [1,2]. LS is classically described as more frequent in females than in males, with two peaks of incidence, in prepubertal age and late adulthood [3]. However, current evidence suggests such condition is probably more underestimated than rare, as traditionally thought [4–7]. White atrophic patches are considered the hallmark of the disease. However, erythema, erosions, fissures, and post-inflammatory hyperpigmentation are also common findings in LS patients. While LS is more commonly observed in genital and perianal areas, extragenital regions such as trunk and thighs can also be affected, posing a great challenge in terms of differential diagnosis [8,9]. Possible complications include the involvement of adjacent structures (e.g., urethra, vagina), with subsequent urinary and/or sexual dysfunction, and the occurrence of squamous cell carcinomas [10,11]. Despite not being a life-threatening condition, LS deeply impacts the daily life and psychological well-being of affected patients. In particular, itching emerges as a defining symptom of LS, causing considerable distress and discomfort [12,13]. Other frequently reported symptoms include pain, soreness, burning, and dyspareunia. Scratching exacerbates the skin inflammation, leading to fissuring and eventually bleeding [14].

The diagnosis of LS is generally clinical, but a biopsy is often required to confirm the condition. Misdiagnoses are not an uncommon, with diagnostic delay deeply impacting patient's quality of life [15]. Living with a chronic and often misunderstood condition can lead to anxiety, depression, and reduced self-esteem [16,17]. Notwithstanding ongoing research efforts, the exact etiology of LS remains elusive. Immune factors, hormonal imbalances, and genetic predisposition may contribute to its development [18–20].

Topical corticosteroid creams or ointments are initially prescribed to reduce inflammation and alleviate itching [21]. In some cases, other immunomodulatory medications may also be recommended to help manage the condition, such as topical calcineurin inhibitors or systemic immunosuppressants [22]. Despite optimal treatment, LS often poses significant challenges in terms of symptom control and management, since conventional therapies lead to limited success in a non-negligible proportion of cases, and complete remission of signs and symptoms remains an unreachable goal for most patients. Given that no definitive cure is currently available, LS represents an expanding field of research. More in detail, platelet-rich plasma (PRP) and adipose-tissue derived stromal cell (ADSCs) therapy have emerged as promising approaches in the management of LS [23,24].

The aim of the present study was to provide an overview of the population of patients followed up at tertiary referral center, with a particular focus on more severe forms of the disease, in terms of complications, comorbidities, and therapeutic approaches.

Materials and Methods

We performed a single-center retrospective observational study. The study was approved by the local Ethics Committee (Protocol LS-ASM 661/2023 approved on 12/12/2023) and conducted in accordance with the principles of the Declaration of Helsinki. We collected and analyzed clinical data on a cohort of patients followed up at our center for LS for two years (between January 2022 and December 2023). Patients were enrolled according to the following inclusion criteria: established diagnosis of LS, age>18. Clinical data were extracted from electronic health records (EHR). For each enrolled subject, we collected the following information: age, sex, diagnosis, disease localization (genital/extragenital), comorbidities, ongoing treatments, previous therapies, signs of LS (hypopigmented patch/plaques, dyschromia, erythema, fissures/erosions, stenosis, fibrosis, atrophy, presence of lesions clinically suspicious for cutaneous squamous cell carcinomas -cSCCs), LS-related symptoms (burning, itching, pain, dyspareunia, dysuria, dyschezia), and response to treatment (stable/improved/worsened). Clinical data were anonymized and collected into an Excel file (Microsoft Office version 16.77). Fisher's exact test was used to examine the relationships between qualitative variables. Numerical data are expressed as mean ± standard deviation or median (range) and qualitative data as frequency (percentage). Student's t-test was used to assess differences for continuous variables between groups.

Results

In total, 46 adult patients affected by LS were included in the present study. Of them, 15 were males and 31 were females, with a M:F ratio of approximately 1:2. Mean age was 58.8 years, in the absence of significant differences between the two sexes. Most of the patients had disease localization in the genital area (n= 41), but three subjects presented with extragenital LS alone. Two-thirds of the cases (n=31, 67%) had exclusively genital involvement, while eight subjects also experienced perianal involvement (7F, 1M). Patient characteristics are summarized in Table 1 (For more detailed data see Supplementary Table 1).

Extragenital LS and/or morphea were present in nine cases. Up to one-third of the subjects (n=13) had other concomitant immune mediated disorders, including lichen planopilaris (LPP), lichen planus (either with oral, cutaneous, or nail involvement), psoriasis, chronic urticaria, autoimmune thyroiditis, vitiligo, atopic dermatitis, alopecia areata,

Table 1. Patient Demographics and Clinical Characteristics.

	M	F	TOT
N pts	15	31	46
Mean Age (y)	57.8	59.2	58.8
Genital LS	14	29	43
Perianal LS	1	7	8
Extragenital LS/mor	2	7	9
AI comorb	3	10	13
Oncol comorb	1	6	7
Treatment			
tCS	12	30	42
tCNI	1	19	20
Emollients	6	15	21
tVitE	5	22	27
Oral suppl	0	14	14
PhotoTp	1	1	2
Syst TT	3	5	8
PRP	0	8	8
SVF	0	4	4
surgery	7	0	7

Data are indicated as absolute frequencies and are subdivided according to patient sex. Abbreviations. N: number; AI: autoimmune; comorb: comorbidities; tCS: topical corticosteroids; tCNI: topical calcineurin inhibitors; tVitE: topical vitamin E; suppl: supplements; PhotoTp: phototherapy; Syst TT: systemic treatment; PRP: platelet-rich plasma; SVF: stromal vascular fraction.

Sjogren syndrome, and cryoglobulinemia. Not surprisingly, a significant proportion (n= 4) of this subset of patients had more than one of these immune-mediated disorders. Oncological comorbidities were also present in seven cases, including cutaneous basal cell carcinoma, abdominal sarcoma, pituitary adenoma, uterine cervix carcinoma, and perianal extramammary Paget's disease. Interestingly, no case of genital squamous cell carcinoma was detected. Although not statistically significant, autoimmune comorbid disorders were found to be slightly more prevalent in females than in males, as were extragenital disease and concomitant neoplasms.

The most frequently reported symptoms included itching, soreness, burning, and dyspareunia. Erythema, hypopigmented patches, erosions, and atrophy were common skin findings (Table 2). Itching and atrophy were particularly frequent in females ($P < 0.05$). In male subjects, preputial involvement was present in the vast majority of cases (n=13), with phimosis being the main reported complication (n=11). Glans involvement (either as erythema or as dyschromic changes) was detected in five subjects, three of whom also displayed disease localization at the external urethral orifice. Two patients had urethral stenosis requiring urological consultation (1M, 1F).

Table 2. LS-Related Signs and Symptoms, Stratified according to Patient Sex. Data are indicated as absolute frequencies.

	F	M	TOT
Symptoms			
itch/pruritus	22	1	23
burning	10	3	13
soreness	9	3	12
pain	3	2	5
dyspareunia	7	1	8
Signs			
erythema	13	7	20
labial fusion/phymosis	23	13	36
hyperpigmentation	7	1	8
hypopigmentation	13	3	16
atrophy	13	1	14
erosions/fissures	9	2	11

A short course of topical therapy was generally prescribed at the first visit. Topical corticosteroids (CS) were prescribed as first-choice therapy in nearly all cases, with clobetasol ointment being the preferred formulation. Daily application was generally suggested over the first month. Some patients (n=20), especially when atrophy was present, switched to topical calcineurin inhibitors (CNI) at follow-up visits. Decalage and eventual discontinuation of CS/CNI was achieved in most patients after 3–6 months, and patients were given instructions on how to recur to topical CS as needed. Oral supplements were also added to topical treatment in 14 cases and were well tolerated by patients. Most frequently prescribed supplements included natural extracts with anti-inflammatory and/or antioxidating properties, collagen, and vitamins E and A. Topical vitamin E and/or emollients were prescribed to be applied daily either in association with topical CS or as stand-alone maintenance therapy.

Alternative treatments were offered to the following patient categories: 1) refractory to conventional therapy; 2) affected by immune-mediated comorbidities requiring different treatments; 3) developing LS-related complications; 4) with extragenital involvement. Possible options included surgery (especially circumcision in male patients), systemic corticosteroids, antihistamines, traditional immunosuppressant drugs (e.g., methotrexate, cyclosporine), phototherapy, biologic drugs (omalizumab, dupilumab, ixekizumab), platelet-rich plasma (PRP), lipofilling and/or use of stromal-vascular fraction (SVF), and photodynamic therapy (PDT).

As for the surgical options, circumcision was performed in seven cases, while two patients refused the intervention despite surgical indication. One subject underwent concomitant meatoplasty.

Systemic corticosteroids were rarely prescribed, but monthly injections of triamcinolone were indicated in a patient with concomitant LPP and nail and oral LP. Phototherapy was the treatment of choice in cases of extragenital LS or morphea refractory to topical corticosteroids. Other systemic treatments, either biologic or not, were commonly prescribed due to patient comorbidities such as psoriasis, chronic urticaria, or atopic dermatitis (n=7). Not surprisingly, patients mostly reported a beneficial effect also on genital symptoms.

PDT was prescribed to a patient with refractory genital LS wishing not to undergo injective or systemic treatments. Homologous PRP was efficiently employed in eight cases of refractory genital LS; patients generally required from three up to five treatment sessions to achieve clinical improvement. In one case, sustained relief from LS-related symptoms was not achieved after PRP treatment; the patient was therefore treated with SVF, with partial benefit. SVF injection, performed by a skilled plastic surgeon under local anesthesia, was offered to four patients in total. This treatment was effective in reducing the symptom burden of around 50-70% according to patient judgement after a single procedure. No significant adverse events were recorded after either PRP or SVF injection, except for moderate pain at the injection site. Mild abdominal tenderness/soreness was also sometimes reported following fat tissue collection for SVF injection. One patient experienced reactivation of HSV2 infection following the procedure and was therefore prescribed systemic acyclovir. Globally, all the mentioned treatments allowed us to maintain patients on topical emollients only and corticosteroids as needed, with good control of LS-related symptoms, but no long-term follow-up data are available to date.

Discussion

This study investigated the demographic characteristics, clinical presentation, and treatment outcomes of 46 patients with lichen sclerosus (LS) referred to a single center between January 2022 and December 2023. The majority of patients were females, with genital involvement being the most common presentation. Interestingly, a subset of patients exhibited extragenital LS and/or morphea, and a significant proportion had concomitant immune-mediated disorders as well as oncological comorbidities. In our analysis, extragenital LS and morphea were considered as a single category not only for their overlapping clinical and histological features, but also due to the compresence of both histologically confirmed diagnoses in a subset of patients (n=3) [25].

In line with previous data suggesting an association between LS and autoimmunity, we detected immune-mediated comorbidities in around one-third of the patients [26]. The coexistence of LS with other immune-mediated disorders suggests a shared underlying pathogenesis involving dysregulated immune responses [2,27]. The presence of extragenital LS and/or morphea in some patients further supports the notion of systemic immunological dysregulation [9,18]. In particular, a shift towards a Th1 response together with the production of specific pro-inflammatory mediators could contribute to the occurrence of the disease [28–30]. Recent reports suggest interleukin-1 (IL1), IL4, IL10, IL12, transforming growth factor b (TGFb), and interferon γ (IFNγ) possibly play a role in this setting [31–33]. LS likely represents a localized manifestation of broader immune dysregulation, with autoimmune mechanisms potentially playing a role in its pathogenesis [34]. Further research is needed to elucidate the precise immunological mechanisms underlying LS and its potential systemic implications, which could pave the way for targeted therapeutic interventions addressing the underlying immune dysregulation.

The most frequently reported symptoms included itching, soreness, burning, and dyspareunia, while common skin findings comprised erythema, hypopigmented patches, erosions, and atrophy

Our data confirm topical corticosteroids, particularly clobetasol ointment, as the mainstay of therapy, with adjunctive use of topical calcineurin inhibitors in a large part of the cases [22]. Oral supplements, including anti-inflammatory and antioxidative agents, seem to bring beneficial effects when prescribed alongside topical treatment. Alternative therapies such as surgery, systemic corticosteroids, phototherapy, and biologic drugs were offered to patients refractory to conventional therapy and those with LS-related complications. Novel treatments such as PRP and SVF injection showed promise in refractory cases [35]. Although generally well tolerated, minor adverse events such as injection site pain and abdominal soreness were reported. Overall, alternative treatments enabled the maintenance of patients on topical emollients and corticosteroids as needed, providing good control of LS-related symptoms. However, the lack of long-term follow-up data warrants further investigation into the efficacy and safety of these interventions [17,36].

One of the limitations of our study is probably the reliance solely on dermatological electronic records for the detection of LS cases, potentially leading to an underestimation of its prevalence. In fact, LS commonly affects anatomical regions beyond the mere expertise of dermatologists, such as the genitalia, necessitating collaboration with specialists in urology and gynecology. Without access to pathology reports and multidisciplinary assessment, atypical cases of LS may be missed or misdiagnosed. Incorporating data from urological, gynecological, and pathological evaluations will be crucial for future studies aimed at comprehensive epidemiological assessment of LS [37]. Moreover, a holistic approach involving interdisciplinary collaboration will be essential to

ensure timely recognition, appropriate treatment, and a better understanding of the full spectrum of LS manifestations.

Conclusions

Our study sheds light on the diverse clinical presentation and management strategies of LS. We observed a predominance of genital involvement, often accompanied by extragenital LS and comorbid immune-mediated disorders. Topical corticosteroids remain the mainstay of therapy, supplemented by alternative treatments in refractory cases. PRP and SVF appear to be the most effective strategies. Collaboration among dermatologists, urologists, gynecologists, and pathologists is essential for accurate diagnosis and optimal management of LS. Further research is warranted to elucidate the underlying immunological mechanisms and to explore long-term efficacy and safety of emerging treatment modalities.

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