Acta Derm Venereol 2013; 93: 238–241

Included in the theme issue:
VENEREOLOGY – NOT TO BE FORGOTTEN
Acta Derm Venereol 2013; 93: 216–256

CLINICAL REPORT

Association of Autoimmune Diseases with Lichen Sclerosus in 532 Male and Female Patients

Alexander KREUTER, Yulia KRYVOSHEYEVA, Sarah TERRAS, Rose MORITZ, Katrin MÖLLENHOFF, Peter ALTMEYER, Nina SCOLA and Thilo GAMBICHLER

Connective Tissue Disease Research Unit of the Department of Dermatology, Venereology, and Allergology, Ruhr-University Bochum, Bochum, Germany

Lichen sclerosus is a relatively common chronic inflammatory skin disease that predominantly affects the anogenital area. Accumulating evidence indicates that lichen sclerosus in women may be associated with other autoimmune disease, whereas this association seems to lack in male patients. We retrospectively evaluated the prevalence of autoimmune diseases and serological parameters indicative for autoimmunity in male and female patients with lichen sclerosus. Of the 532 patients (396 women, 136 men; 500 adults, 32 children; mean age: 49 years; range 1–89 years; female:male ratio 3:1), 452 (85%) had genital and 80 (15%) had extragenital disease. In women, lichen sclerosus was significantly more often associated with at least one autoimmune disease as compared to men (odds ratio [OR] 4.3, 95% confidence interval [CI] 1.9–9.6; $p<0.0001$). Moreover, female patients with lichen sclerosus had sinificantly more often associated autoimmune thyroid diseases (OR 4.7, 95% CI 1.8–11.9; $p<0.0002$), antithyroid-antibodies (OR 2.7, 95% CI 1.1–6.5; $p=0.023$), and elevated autoantibodies (OR 4.1, 95% CI 1.9–9.3; $p<0.0001$) as compared to male patients. This observation is suggestive for a different pathogenetic background in male and female patients.

Key words: antinuclear antibodies; autoimmune disease; lichen sclerosus; thyroid disease.

Accepted Sep 17, 2012; Epub ahead of print Nov 29, 2012

Acta Derm Venereol 2013; 93: 238–241.

Prof. Alexander Kreuter, Connective Tissue Disease Research Unit of the Department of Dermatology, Venereology, and Allergology at Ruhr-University Bochum, Gudrunstrasse 56, DE-44791 Bochum, Germany. E-mail: a.kreuter@derma.de

Lichen sclerosus (LS) is a relatively common chronic inflammatory skin disease that predominantly affects the anogenital region. LS has a clear female preponderance, with female:male ratios of 6–10:1 reported in the literature (1). The exact prevalence of LS is unknown, but estimates range from 1 in 300 to 1 in 1,000 among patients referred to a dermatology department (2). However, most experts agree that these numbers probably underestimate the true prevalence of LS. Most studies of LS have been in white subjects, but there have also been reports on LS in people of other ethnicities (1). LS has a bimodal onset of presentation, with a first peak in prepubertal girls and boys and a second peak in postmenopausal women and adult men (2, 3). Extragenital disease seems to affect approximately 15% of patients, and most frequently occurs in adult women, involving classical sites such as the upper trunk, axillae, and lateral thighs (4). In contrast, extragenital LS in men is extremely rare (5). Accumulating evidence indicates that LS has an autoimmune aetiology. Antibodies against the basement membrane zone have been found in the sera of patients with LS, and a high proportion of patients have specific antibodies targeting extracellular matrix protein-1 (6, 7). Several previous reports have demonstrated that LS might be associated with other autoimmune disorders, further supporting the hypothesis of an autoimmune background. As LS mostly affects women, the majority of these studies investigated autoimmune associations in vulvar LS (8–11). Interestingly, a recent retrospective analysis of the clinical parameters of male genital LS failed to demonstrate an association with autoimmunity (5). This discrepancy prompted us to retrospectively evaluate the prevalence of associated autoimmune disorders and serological parameters of autoimmunity in a large cohort of patients with LS who were diagnosed and treated for connective tissue diseases at the outpatient clinic of the Department of Dermatology, Venereology, and Allergology at Ruhr University Bochum. The main purpose of this study was to explore possible gender differences in the pattern of autoimmunity, which could point to a divergent pathogenetic background in male and female LS.

MATERIALS AND METHODS

Patients

A retrospective review of the digital databases of LS patients who attended the outpatient clinic for connective tissue diseases of the Department of Dermatology at Ruhr University Bochum was performed. The observation period was 12 years (1 January 2000 through 1 January 2012). The study was approved by the ethics review board of the Ruhr University of Bochum.

Clinical examination and anamnesis of autoimmune-related disease

To be eligible for this retrospective study, the typical clinical criteria for LS had to be present, as previously published (1, 4).

Table I. *Demographic characteristics of the 532 patients with lichen sclerosus*

Characteristic	Value
Age at diagnosis (overall), years, mean (range)	49 (1–89)
Males	136
Adult men	134
Boys[a]	2
Age at diagnosis, years, mean (range)	49.4 (7–89)
Female	396
Adult women	366
Girls[a]	30
Age at diagnosis, years, mean (range)	48.8 (1–85)
F/M ratio	3:1

[a]Younger than 14 years of age. F: female; M: male.

Table II. *Anatomical location of disease of the 532 patients with lichen sclerosus*

Location	Overall ($n=532$) *n* (%)	Females ($n=396$) *n* (%)	Males ($n=136$) *n* (%)
Anogenital	452 (85.0)	322 (81.3)	130 (95.6)
Extragenital	80 (15.0)	74 (18.7)	6 (4.4)
Back	19 (23.8)	19 (25.8)	0
Shoulder	7 (8.8)	7 (9.5)	0
Thighs	13 (16.3)	12 (16.2)	1 (16.7)
Chest	18 (22.5)	17 (23.0)	1 (16.7)
Abdomen	4 (5.0)	4 (5.4)	0
Proximal extremities	19 (23.8)	15 (20.3)	4 (66.7)

Punch biopsies for histopathological analysis were only taken in patients with an inconclusive clinical status. In all patients, a detailed medical history (including current medication and co-morbidities), physical examination, and clinical inspection of the entire skin were performed. All patients were asked about associated autoimmune diseases, including autoimmune thyroid diseases (Hashimoto thyroiditis and Graves disease), autoimmune skin diseases (vitiligo, alopecia areata, localized scleroderma, systemic sclerosis, cutaneous and systemic lupus erythematodes, dermatomyositis, pemphigus, bullous pemphigoid, and psoriasis), inflammatory bowel disease (Crohn's disease and ulcerative colitis), as well as autoimmune rheumatic diseases (rheumatoid arthritis, ankylosing spondylitis and Sjögren syndrome). Most experts nowdays consider psoriasis and inflammatory bowel disease to belong to the spectrum of autoimmune diseases.

Serological evaluation

The standard serological analysis included a complete blood cell count, antinuclear antibodies (ANA; a titre $\geq$1:80 was considered as positive), screening for extractable nuclear antibodies (ENA), including anti-Ro and anti-La antibodies, anti-Smith antibodies, anti-U1-ribonucleoprotein antibodies, anti-histone antibodies, anti-SCL-70 antibodies, anti-centromere antibodies, and anti-Jo-1 antibodies), anti-double-stranded deoxyribonucleic (anti-Ds-DNA) antibodies, anti-smooth muscle antibodies (ASMA), rheumatoid factor, anti-cyclic citrullinated peptide antibodies, circulating immune complexes, anti-thyroid antibodies (thyroid peroxidase and anti-human thyroglobulin antibodies), complement components 3 and 4, C-reactive protein, and routine blood chemistry testing.

Statistical analysis

Analysis of data was performed using the statistical package MedCalc (MedCalc Software, Mariakerke, Belgium). The main objective was to compare the frequencies of associated autoimmune diseases and laboratory parameters in male and female patients with LS. The Fisher's exact test was used. Furthermore, the odds ratio (OR) including the 95% confidence interval (CI) was calculated. A p-value <0.05 was considered significant.

RESULTS

Demographic characteristics

A total of 532 patients with LS were diagnosed and treated at the Department of Dermatology at Ruhr University Bochum from 1 January 2000, through 1 January 2012. Among them, 396 were female (30 girls and 366 adult women) and 136 were male (2 boys and 134 adult men). The mean age of the 532 patients was 49 years. The female:male ratio was 3:1. All demographic characteristics are shown in Table I.

Anatomical location of lichen sclerosus

Of the 532 patients, 452 (85%) had anogenital and 80 (15%) had extragenital disease. In men, LS was located exclusively in the genital area (glans, prepuce and penile shaft). None of the male patients had perianal disease. The percentage of extragenital LS was significantly higher in women compared with men (74 women (18.7%) vs. 6 men (4.4%), $p=0.000021$). The most frequent sites of extragenital LS were the back, chest and proximal extremities. Three (10%) of the 30 girls and none of the 2 boys had extragenital LS. All data on the anatomical location of LS in the 532 patients is depicted in Table II.

Table III. *Prevalence of associated autoimmune diseases of the 532 patients with lichen sclerosus*

Disease	Overall ($n=532$) *n* (%)	Females ($n=396$) *n* (%)	Males ($n=136$) *n* (%)	*p*-value (females vs. males)	Odds ratio (95% CI)[b]
With at least one autoimmune disease	82 (15.4)	75 (18.9)	7 (5.1)	<0.0001	4.3 (1.9–9.6)
Autoimmune thyroid disease[a]	65 (12.2)	60 (15.2)	5 (3.8)	0.0002	4.7 (1.8–11.9)
Rheumatoid arthritis	4 (0.8)	3 (0.8)	1 (0.7)	1	
Localized scleroderma	9 (1.7)	9 (2.3)	0	0.12	
Ulcerative colitis	1 (0.2)	0	1 (0.7)	0.3	
Psoriasis	3 (0.6)	3 (0.8)	0	1	

[a]Active and inactive Hashimoto thyroiditis and Graves' disease as well as hypothyreosis and hyperthyreosis related to both diseases were considered as autoimmune thyroid disease.

[b]Odds ratios and 95% confidence intervals (CI) are given only for statistical significant parameters.

Prevalence of associated autoimmune diseases in male and female patients with lichen sclerosus

Of the whole LS cohort, 82 (15.4%) had at least one autoimmune disease. Female patients had significantly more often at least one autoimmune disease compared with male patients (18.9% vs. 5.1%, odds ratio (OR) 4.3, 95% confidence interval (CI) 1.9–9.6, $p < 0.0001$). Moreover, autoimmune thyroid diseases were significantly more frequent in women compared with men (15.2% vs. 3.8%, OR 4.7, CI 1.8–11.9, $p = 0.0002$). Other associated autoimmune diseases included rheumatoid arthritis, localized scleroderma, ulcerative colitis, and psoriasis, but the differences between women and men were not statistically different. None of the patients had vitiligo, alopecia areata or autoimmune diseases that have been previously reported in association with LS. There was no significant difference in the prevalence of autoimmune diseases when comparing patients with genital and extragenital LS. The prevalence of associated autoimmune diseases is shown in Table III.

Serological parameters of autoimmunity in male and female patients with lichen sclerosus

Similar to the analysis of autoimmune diseases, autoantibodies were significantly more often found in female patients compared with male patients with LS (OR 4.1, CI 1.9–9.3, $p < 0.0001$, cumulative analysis of ANA, ENA, anti-dsDNA, and ASMA). Except for one woman with very high ANA (titre 1:1280), all patients had ANA titres lower than 1:320. Among the 12 ENA-positive women with LS, 5 had anti-Ro-antibodies, 2 had anti-histone-antibodies, 1 had anti-SCL-70-antibodies, and 4 had ENA not further specified. The only ENA-positive men had ENA not further specified as well. Anti-thyroid-antibodies were also significantly more frequent in women compared with men (11.1% vs. 4.4%, OR 2.7, CI 1.1–6.5, $p = 0.023$). There were no significant differences in circulating immune complexes, C3 and C4 hypocomplementaemia, and rheumatoid factor. All relevant serological autoimmune parameters are listed in Table IV.

DISCUSSION

Unproven consensus exists among experts that LS is an autoimmune disease. Circulating antibodies targeting extracellular matrix 1-protein and the basement membrane zone (mainly BP180 and 230) have been found in LS, and associated autoimmune diseases are frequent (6, 7). Thus far, 3 studies exist that evaluated the prevalence of autoimmune diseases in LS, and all of them exclusively analysed women (9, 11, 12). Harrington & Dunsmore (12) have shown that 17 of 50 female patients (34%) with LS had at least 1 autoimmune disease, and pernicious anaemia and alopecia areata were most commonly found. Meyrick Thomas et al. (9) reported a lower percentage (21.5%) of autoimmune diseases in 350 patients with vulvar LS. The most frequent autoimmune disease in this cohort was alopecia areata (9%). The most recent study, on 190 female patients treated at the vulval clinics in Oxfordshire, UK, revealed that 28.4% of patients had at least one autoimmune disease (11). Among the individual autoimmune diseases that were significantly more present in LS compared with controls were thyroid disease (16.3% vs. 7.9%), alopecia areata (2.6% vs. 0.1%), morphea (1.5% vs. 0%) and pernicious anaemia (3.6% vs. 0.1%).

To our best knowledge, the present study is the first that compares the frequency of autoimmune disease in women and men with LS, and is the largest cohort of LS patients so far published in the literature. When comparing the prevalence of autoimmune diseases in women found in this study with the previously published data, the percentage of at least one autoimmune disease

Table IV. *Serological parameters of autoimmunity of the 532 patients with lichen sclerosus*

Parameter	Overall ($n = 532$) n (%)	Females ($n = 396$) n (%)	Males ($n = 136$) n (%)	p-value (females vs. males)	Odds ratio (95% CI)[b]
ANA	39 (7.3)	38 (9.6)	1 (0.7)		
ENA	13 (2.4)	12 (3.0)	1 (0.7)	<0.0001	4.1 (1.9–9.3)
Anti-dsDNA	7 (1.3)	6 (1.5)	1 (0.7)		
ASMA	21 (3.9)	17 (4.3)	4 (2.9)		
Anti-thyroid-AB[a]	50 (9.4)	44 (11.1)	6 (4.4)	0.023	2.7 (1.1–6.5)
CIC	46 (8.6)	34 (8.6)	12 (8.8)	1	
C3	13 (2.4)	11 (2.8)	2 (1.5)	0.8	
C4	3 (0.6)	2 (0.5)	1 (0.7)		
RF	7 (1.3)	7 (1.8)	0	0.2	

[a]Thyroid peroxidase (> 6.6 U/ml was considered as pathological) and anti-human thyroglobulin (> 115 U/ml was considered as pathological) were considered as anti-thyroid-antibodies.

[b]Odds ratios and 95% confidence interval (CI) are given only for statistical significant parameters.

ANA: antinuclear antibody (a titre of > 1:320 was considered positive); Anti-thyroid-AB: anti-thyroid-antibodies; ASMA: anti-smooth muscle antibodies; CIC: circulating immune complexes (> 4.4 µg/ml was considered as pathological); C3: C3-hypocomplementaemia (< 90 mg/dl was considered as C3-hypocomplementaemia); C4: C4-hypocomplementaemia (< 10 mg/dl was considered as C4-hypocomplementaemia); dsDNA: double-stranded DNA; ENA: extractable nuclear antigens; RF: rheumatoid factor (> 14 U/ml was considered as pathological).

(18.9%) in our cohort is somewhat lower, but the prevalence of autoimmune thyroid disease (15.2%) is very similar to the data of Cooper et al. (11) (16.3% of women with LS and only 7.9% of healthy controls had thyroid disease). Interestingly, none of the LS patients of the present study had vitiligo, alopecia areata, or pernicious anaemia, which can probably be explained by regional differences. High rates of auto-antibodies (42–74%) in female patients with LS have been previously reported in the literature (9, 12). In line with the aforementioned observation, increased autoantibody levels were found in our female LS cohort, but the percentages were lower (Table IV). Different antibody detection methods probably explain this variation.

This study has clearly shown that female and male patients differ significantly in their percentages of autoimmune diseases, especially autoimmune thyroid disease, as well as autoantibody levels (Tables III and IV). When comparing the male patients with LS of this study with the healthy control group of 922 patients reported by Cooper et al. (11), the prevalence of autoimmune diseases and autoimmune thyroid disease of our men with LS was even lower than that of the general population. Therefore, autoimmunity seems unimportant in male LS. This is in line with a recent study on 329 male patients with LS that found autoimmune diseases in only 23 (7%) of patients (5). It has been speculated that urine impacting on susceptible genital epithelium might be the predominant causative factor in male genital LS. It is likely that urine in uncircumcised men that dribbles from a dysfunctional naviculomeatal valve and pools in the inner part of the prepuce finally initiates LS in predisposed individuals (5). This would also explain the typical location of male genital LS (glans and prepuce), the rarity of male extragenital and perianal LS, and the high resolution rate of male LS post-circumcision.

The results reported here should be interpreted in light of the limitations of the study. Although the main objective of this study was the direct comparison of associated autoimmune disease in men and women with LS, we did not include an age- and sex-matched control group. Nevertheless, previous studies clearly demonstrated that autoimmune diseases are significantly more frequent in female LS compared with healthy controls. Moreover, screening for autoimmune diseases and serological examination was only performed once at first presentation. It would be interesting to follow serological autoimmune parameters over time and to determine if these parameters correlate with the activity of disease. In addition, the number of juvenile patients with LS was very low. Thus, we were unable to compare the prevalence of autoimmune disease between adults and children. High rates (21–36%) of family history of autoimmune-related disease in women with LS have been reported previously (9, 11, 12). Unfortunately, this point is not included in the baseline medical history of our LS patients. Finally, our cohort almost exclusively comprised Caucasian patients, and therefore the results of this study might not be generalizable to other ethnics.

In conclusion, by analysing an appropriately large cohort of patients we have shown that female patients with LS frequently have associated autoimmune diseases, especially autoimmune thyroid disease, as well as circulating autoantibodies. In contrast, these features are missing in male patients with LS. This difference is highly suggestive for a divergent pathogenetic background. In daily routine, women with LS should be screened for other autoimmune diseases, whereas such screenings may not be necessary in men.

The authors declare no conflicts of interest.

REFERENCES

1. Powell JJ, Wojnarowska F. Lichen sclerosus. Lancet 1999; 353: 1777–1783.
2. Wallace HJ. Lichen sclerosus et atrophicus. Trans St Johns Hosp Dermatol Soc 1971; 57: 9–30.
3. Lipscombe TK, Wayte J, Wojnarowska F, Marren P, Luzzi G. A study of clinical and aetiological factors and possible associations of lichen sclerosus in males. Australas J Dermatol 1997; 38: 132–136.
4. Neill SM, Lewis FM, Tatnall FM, Cox NH. British Association of Dermatologists' guidelines for the management of lichen sclerosus 2010. Br J Dermatol 2010; 163: 672–682.
5. Edmonds EV, Hunt S, Hawkins D, Dinneen M, Francis N, Bunker CB. Clinical parameters in male genital lichen sclerosus: a case series of 329 patients. J Eur Acad Dermatol Venereol 2012; 26: 730–737.
6. Howard A, Dean D, Cooper S, Kirtshig G, Wojnarowska F. Circulating basement membrane zone antibodies are found in lichen sclerosus of the vulva. Australas J Dermatol 2004; 45: 12–15.
7. Oyama N, Chan I, Neill SM, Hamada T, South AP, Wessagowit V, et al. Autoantibodies to extracellular matrix protein 1 in lichen sclerosus. Lancet 2003; 362: 118–123.
8. Harrington CI, Dunsmore IR. An investigation into the incidence of auto-immune disorders in patients with lichen sclerosus and atrophicus. Br J Dermatol 1981; 104: 563–566.
9. Meyrick Thomas RH, Ridley CM, McGibbon DH, Black MM. Lichen sclerosus et atrophicus and autoimmunity: a study of 350 women. Br J Dermatol 1988; 118: 41–46.
10. Birenbaum DL, Young RC. High prevalence of thyroid disease in patients with lichen sclerosus. J Reprod Med 2007; 52: 28–30.
11. Cooper SM, Ali I, Baldo M, Wojnarowska F. The association of lichen sclerosus and erosive lichen planus of the vulva with autoimmune disease: a case-control study. Arch Dermatol 2008; 144: 1432–1435.
12. Harrington CI, Dunsmore IR. An investigation into the incidence of auto-immune disorders in patients with lichen sclerosus and atrophicus. Br J Dermatol 1981; 104: 563–566.