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Comorbidity of Urogynecological and Gastrointestinal Disorders in Female Patients With Lichen Sclerosus

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Objective: Lichen sclerosus (LS) is a chronic inflammatory disease with a significant impact on quality of life. The aim of this cross-sectional case-control study was to characterize concomitant urogynecological and gastrointestinal disorders in female patients with LS.

Methods: A medical records search between 2004 and 2012 yielded 455 women and girls (mean age 64 years) with LS. The study cohort was compared with a 10-fold age- and sex-matched control cohort. Gynecological cancers and their precursors; gynecological, urinary, and gastrointestinal disorders; and pain syndromes were evaluated.

Results: The well-known association between LS and increased risk of vulvar cancer and its precursors was also found in our study (relative risk [RR] = 100.0; $p < .001$ and high-grade squamous intraepithelial lesions RR = 110.0; $p < .001$, respectively), but we also found an increased risk for cervical cancer (RR = 6.0; $p = .005$) and endometrial cancer (RR = 2.9; $p < .001$). Gynecological pain syndromes such as dyspareunia (RR = 20.0; $p < .001$) and interstitial cystitis (RR = 5.0; $p < .001$) and urinary incontinence (RR = 4.8; $p < .001$) were also increased. Among gastrointestinal disorders, we found increased risk for celiac disease (RR = 6.8; $p < .001$), diverticular intestine diseases (RR = 1.9; $p < .001$), functional intestinal disorders (RR = 2.3; $p = .003$), and anal and rectal fissures (RR = 2.4; $p = .046$).

Conclusions: We found that female patients with LS have an increased risk for gynecological cancers as well as for several urogynecological and gastrointestinal disorders. Increased awareness is required to identify and treat these concomitant disorders.

Key Words: lichen sclerosus, gynecological cancer, gynecological disorder, pain syndrome, urogenital disorder, gastrointestinal disorder

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Lichen sclerosus (LS) is a chronic inflammatory disease that predominantly affects the anogenital skin. Its etiology is unknown, although a strong association with autoimmune disease is recognized.¹ An infectious etiology has also been suggested because LS has a genetic predisposition.² The prevalence is estimated to range from 1:300 to 1:1,000³ and is even higher among elderly women.⁴ In general gynecological practice, the prevalence of vulvar LS is estimated at 1.7%⁵; however, the exact prevalence

is difficult to ascertain because some patients remain asymptomatic. The diagnosis of LS is usually clinical.³

An association between vulvar squamous cell carcinoma (SCC) and vulvar LS is well documented. The lifetime risk of vulvar SCC in LS patients is estimated at 4% to 5%.⁶ A recent European study showed a cumulative incidence of vulvar SCC of 6.7% in LS patients after 20 years of follow-up.⁷ The reason for the malignant transformation from LS to SCC remains unknown. Lichen sclerosus has also been associated with a rare vulvar melanoma⁸ and basal cell carcinoma.⁹ In addition, some evidence supports an increased risk of vaginal cancer.¹⁰

Itching and soreness are common symptoms of LS. Post-inflammatory scarring may cause alterations in the vulvar architecture, leading to dyspareunia and sexual dysfunction.¹¹ Generally, LS has a significant impact on quality of life^{12,13} and has been linked to bladder, gastrointestinal, and pain comorbidities,¹⁴ but the research is still limited.

Some studies have suggested that certain vulvar diseases may represent symptoms of a generalized disorder of the pelvic floor as well as of other nearby structures, such as the bladder and bowel.^{15,16} Bladder and bowel disorders include overactive bladder (OAB), urinary incontinence, inflammatory bowel disease, constipation, and irritable bowel syndrome.^{14,17} Lichen sclerosus patients have been shown to have significantly more OAB, a greater prevalence of both stress and urgency incontinence, and a higher prevalence of irritable bowel syndrome.¹⁷ However, coexisting celiac disease has been reported in adults in only a case report of 1 LS patient.¹⁸

The aim of the present study was to evaluate the comorbidity of LS patients. We explored the risk of malignancies as well as the risks of urogynecological and gastrointestinal disorders. We hypothesized that not only are the risks of malignancies increased, but LS patients are also more likely to experience several benign urogynecological and gastrointestinal diseases and conditions.

METHODS

This cross-sectional case-control study included 455 women and girls with a diagnosis of LS who were treated for any reason at University Hospital from 2004 to 2012. Patients with a diagnosis of LS were identified by searching electronic medical records for International Classification of Diseases 10 (ICD-10) code L90.0. The diagnosis of LS was based on a clinical examination made by a specialist in gynecology. Among 455 LS patients, 259 patients had clinical diagnosis and 196 patients had histology-proven LS.

A 10-fold age- and sex-matched cohort with no diagnosis of LS served as a control cohort. This cohort was randomly selected from the University Hospital patient register. The health care district consists of more than 470,000 residents, and University Hospital serves as a tertiary clinic in 2 hospital districts.

The electronic patient register contains clinical data for all patients who visit public hospitals in the hospital district and includes administrative information, personal data, diagnosis, and diagnostic and treatment procedures. All diseases occurring in the cohorts during the study period were included. The diseases and conditions of interest were divided into: 1) cancers and their precursors (vulvar cancer, cervical cancer, endometrial cancer,

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IRB status: This study is approved by Turku University Review Board (date of IRB approval December 5, 2018, IRB number T05/047/18).

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ovarian cancer, breast cancer, vulvar high-grade squamous intraepithelial lesions [HSIL], differentiated-type vulvar intraepithelial neoplasia [dVIN], cervical squamous intraepithelial lesion [SIL], 2) gynecological disorders (menorrhagia and postmenopausal bleeding [combined as menstrual disorders], inflammation of the vagina and vulva, anogenital condyloma, and/or vulvar low-grade squamous intraepithelial lesion [LSIL]), 3) pain syndromes (dyspareunia, interstitial cystitis), 4) urinary disorders (urinary incontinence), and 5) gastrointestinal disorders (diseases of the lip and oral mucosa, diverticular disease of the intestine, functional intestinal disorders, inflammatory bowel diseases like Crohn disease and ulcerative colitis, fissures of the anal and rectal regions, and celiac disease).

This study was approved by the clinical research center.

Statistical Analyses

We compared the prevalence of diagnoses between LS patients and controls by calculating relative risks (RRs), confidence intervals (95% CIs), and *p* values for each diagnosis using the Pearson chi-square test. Patient age was calculated at the index date, which was chosen as the first occurrence of the LS diagnosis code in the electronic health records. All statistical tests were 2-tailed, and *p* < .05 was considered statistically significant. Statistical analysis was performed using R Statistics version 3.0.2 (Free Software Foundation, Boston, MA). Analysis of the patients with biopsy-proven LS was also conducted.

RESULTS

A total of 455 women and girls with a diagnosis of LS were identified in the medical records registry. Overall, 93.4% of the LS patients and the controls lived in the hospital district. The mean age of the LS patients was 64 years (range = 6–104), and the age distribution is shown in Figure 1. The population of women and girls in the hospital district is approximately 250,000; thus, the prevalence of those referred for LS was 1.8:1,000 (95% CI = 1.6–2.0).

Gynecological Cancers and Precursors and LS

We found an increased risk for vulvar cancer in the LS patients compared with the control cohort (RR = 100.0; 95% CI = 50.9–196.4; *p* < .001). Twenty LS patients had a diagnosis of vulvar

cancer, for a prevalence of 4.4%. Eighteen cases (90%) were histologically verified as SCC, and the other 2 were unspecified. Vulvar HSIL was increased in the LS patients (RR = 110.0; 95% CI = 14.2–850.1; *p* < .001). We also identified an additional 8 (1.8%) cases of vulvar dVIN in the LS patients, but none in the control cohort (Table 1).

The risk of cervical cancer was higher (RR = 6.0; 95% CI = 1.7–21.1; *p* = .005) among LS patients, although only 3 cases were detected overall. The risk of cervical SIL was slightly higher in the LS patients than in the control cohort (RR = 2.3; 95% CI = 1.0–5.0; *p* = .044). One LS patient had vaginal SCC, but none in the control cohort did. The prevalence of endometrial cancer was also higher among the LS patients (RR = 2.9; 95% CI = 1.6–5.4; *p* < .001). We did not find any associations with any other cancers. (Table 1).

Urogynecological Disorders, Pain Syndromes, and LS

The frequency of different gynecological disorders and uterine pathology, in addition to pain syndromes and urinary disorders, is shown in Table 2. Among the pain syndromes, dyspareunia and interstitial cystitis were diagnosed at higher rates in the LS patients than in the control cohort, even though the prevalences were quite low in both cohorts (1.3%). The RR was increased for dyspareunia (RR = 20.0; 95% CI = 7.5–53.1; *p* < .001) and interstitial cystitis (RR = 5.0; 95% CI = 2.1–12.1; *p* < .001). As for urinary disorders, we found that urinary incontinence was more common in the LS patients, with an RR of 4.8 (95% CI = 3.3–7.0; *p* < .001). Our evaluation of gynecological infections revealed an increased risk of vaginal and vulvar inflammation (RR = 13.1; 95% CI = 9.4–18.2; *p* < .001). Nine of our LS patients had ulcers in genital mucosa. Human papilloma virus (HPV)-related infections in the anogenital area were detected more often in the LS patients than in the control cohort (RR = 3.8; 95% CI = 2.1–6.7; *p* < .001). The risks of menorrhagia and postmenopausal bleeding (combined as menstrual disorders) were also elevated in the LS patients (RR = 2.5; 95% CI = 1.9–3.2; *p* < .001).

Gastrointestinal Disorders and LS

In our study, oral lichen planus was found 10 times more often in LS patients. Oral symptoms were often nonspecific. Among

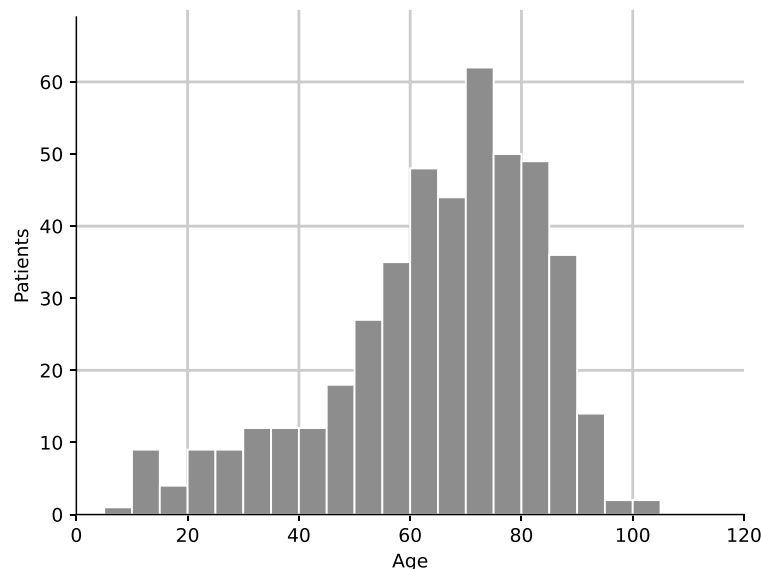


FIGURE 1. Age (years) distribution of 455 female patients with LS.

TABLE 1. Prevalence and Relative Risks of Gynecological Cancers and Precursors Found in 455 Women and Girls With LS and Their 4,550 Controls

Gynecological cancers and precursors	ICD-10	Prevalence in 455 women and girls with LS, % (n)	Prevalence in 4,550 controls, % (n)	RR	95% CI	<i>p</i>
Vulvar cancer	C51	4.4 (20)	0.04 (2)	100.0	50.9–196.4	<0.001
Cervical cancer	C53	0.7 (3)	0.1 (5)	6.0	1.7–21.1	0.005
Endometrial cancer	C54	2.6 (12)	0.9 (41)	2.9	1.6–5.4	<0.001
Ovarian cancer	C56	0.7 (3)	0.6 (26)	1.2	0.4–3.8	0.81
Breast cancer	C50	4.6 (21)	4.3 (198)	1.1	0.7–1.7	0.79
Vulvar HSIL	N90.1 N90.2	2.4 (11)	0.02% (1)	110.0	14.2–850.1	<0.001
Vulvar dVIN	D07.1	1.8 (8)	0.0 (0)	NA	NA	<0.001
Cervical SIL	N87	1.5 (7)	0.7 (31)	2.3	1.0–5.0	0.044

gastrointestinal disorders, we found an increased risk of celiac disease in the LS patients (RR = 6.8; 95% CI = 3.7–12.5; *p* < .001) (Table 2). The risk for diverticular diseases of the intestine (RR = 1.9; 95% CI = 1.3–2.6; *p* < .001), functional intestinal disorders (RR = 2.3; 95% CI = 1.3–4.1; *p* = .003), and anal and rectal fissures was also increased in the LS patients (RR = 2.4; 95% CI = 1.0–5.7; *p* = .046), as was the risk of diseases of the lip and oral mucosa (RR = 4.8; 95% CI = 2.7–8.7; *p* < .001). The risk for inflammatory bowel diseases like Crohn disease or ulcerative colitis was not increased (RR = 1.3; 95% CI = 0.3–5.4; *p* = .77 for Crohn disease and RR = 0.7; 95% CI = 0.2–2.2; *p* = .54 for ulcerative colitis).

Findings in Patients With Biopsy-Proven LS

Our subanalysis included the patients with LS confirmed by histological analysis, and the results are shown in Table 3. The findings were similar to those of the full analysis, but the association with cervical cancer was not confirmed.

DISCUSSION

We verified the previously reported association between LS and vulvar cancer, while also identifying the novel finding of increased risk for other gynecological cancers (e.g., cervical and endometrial cancer). Lichen sclerosis patients were also more likely to experience different benign urogynecological disorders, including inflammation of the vulva and vagina, menorrhagia, and urinary incontinence, as well as pain syndromes like dyspareunia and interstitial cystitis. Lichen sclerosis patients also had a higher risk of gastrointestinal disorders, including celiac disease, diverticular intestinal diseases, functional intestinal disorders, and anal and rectal fissures, suggesting significant comorbidity in LS. Some associations were probably consequences of LS or immunosuppressive LS treatments, but common pathophysiologic pathways are plausible.

Lichen sclerosis patients had increased risk of vulvar cancer, mostly SCCs, as reported previously,^{6–8} but different vulvar malignancies have been reported with LS.⁹ Vulvar SCC may arise by

TABLE 2. Prevalence and Relative Risks of Gynecological and Gastrointestinal Disorders Found in 455 Women and Girls With LS and Their 4,550 Controls

Comorbidity	ICD-10	Prevalence in 455 women and girls with LS, % (n)	Prevalence in 4,550 controls, % (n)	RR	95% CI	<i>p</i>
Gynecological disorders						
Menstrual disorders (menorrhagia and postmenopausal bleeding combined)	N92 N95.0	10.8 (49)	4.4 (200)	2.5	1.9–3.2	<0.001
Inflammation of vagina and vulva	N76	10.3 (47)	0.8 (36)	13.1	9.4–18.2	<0.001
Anogenital condyloma ± vulvar LSIL	A63.0 N90.0	6.6 (30)	0.8 (37)	8.1	5.1–13.0	<0.001
Pain syndromes						
Dyspareunia	N94.1	1.3 (6)	0.1 (3)	20.0	7.5–53.1	<0.001
Interstitial cystitis	N30.1	1.3 (6)	0.3 (12)	5.0	2.1–12.1	<0.001
Urinary disorders						
Urinary incontinence	N39.3 N39.4 R32	6.6 (30)	1.4 (62)	4.8	3.3–7.0	<0.001
Gastrointestinal disorders						
Obesity	E66	7.9 (36)	1.8 (80)	4.5	3.2–6.4	<0.001
Diseases of lip and oral mucosa	K13	2.9 (13)	0.6 (27)	4.8	2.7–8.7	<0.001
Crohn disease	K50	0.4 (2)	0.4 (16)	1.3	0.3–5.4	0.77
Diverticular disease of the intestine	K57	7.5 (34)	4.0 (183)	1.9	1.3–2.6	<0.001
Functional intestinal disorders	K59	3.1 (14)	1.3 (60)	2.3	1.3–4.1	0.003
Celiac disease	K90.0	2.9 (13)	0.4 (19)	6.8	3.7–12.5	<0.001
Ulcerative colitis	K51	0.7 (3)	0.9 (43)	0.7	0.2–2.2	0.54
Fissures of anal and rectal regions	K60	1.3 (6)	0.6 (25)	2.4	1.0–5.7	0.046

TABLE 3. Main Results of Gynecological and Gastrointestinal Disorders Found in 196 Patients With LS Confirmed by Biopsy and Their 10-Fold Age-Matched Cohort

Comorbidity	ICD-10	Prevalence in 196 women and girls with LS, % (n)	Prevalence in 1,960 controls, % (n)	RR	95% CI	<i>p</i>
Vulvar cancer	C51	7.1 (14)	0.1 (2)	70.0	32.7–149.8	<0.001
Cervical cancer	C53	0.5 (1)	0.1 (2)	5.0	0.6–43.3	0.14
Endometrial cancer	C54	3.6 (7)	0.9 (17)	4.1	1.8–9.2	0.001
Vulvar HSIL and/or dVIN	N90.1 N90.2 D07.1	3.6 (7)	0.0 (0)	NA	NA	NA
Celiac disease	K90.0	2.0 (4)	0.3 (6)	6.7	2.2–19.9	0.001
Urinary incontinence	N39.3 N39.4 R32	8.2 (16)	1.6 (31)	5.2	3.0–8.8	<0.001
Dyspareunia	N94.1	1.5 (3)	0.1 (1)	30.0	7.0–128.3	<0.001
Interstitial cystitis	N30.1	2.0 (4)	0.3 (6)	6.7	2.2–19.9	0.001

HPV-associated pathway via vulvar HSIL or by HPV-independent pathway via LS-associated dVIN. Progression of dVIN to vulvar SCC is frequently missed,¹⁹ and the low number of LS patients with SIL diagnosed with dVIN may result from misclassification.⁷ We did not reevaluate the histopathological features of diagnoses of vulvar SIL; however, SIL changes were frequently found, suggesting a need for biopsy and meticulous follow-up in women with LS and any type of SIL.

We also found a slightly increased risk of cervical cancer and cervical SIL in our LS patients. In our country, cervical cancer is a rare disease, with an annual incidence of 6.1/100,000 women (www.cancerregistry.fi), and we identified 3 patients with both cervical cancer and LS. Human papillomavirus is the main risk factor for cervical cancer, and our LS patients showed increases in HPV-related infections in the anogenital area. Immunosuppressive medications, such as topical steroids used in the treatment for LS, could be one explanation, although another could be the existence of an underlying immunodeficiency in LS that allows HPV to thrive. However, we could not totally exclude the fact that the LS patients had more visits rather than the control group, maximizing the probability to evidence HPV-related infections. Nevertheless, HPV infections have been shown to have a role in the development of LS.²⁰ Patients with vulvar cancer related to HSIL have an increased incidence of cervical malignancies due to high-risk HPV.²¹ However, previous cervical HSIL is also a risk factor for both cervical and vulvar cancer, even though only 15% to 17% of invasive vulvar cancer cases in elderly women are associated with high-risk HPV infections.^{22,23} Human papillomavirus might also have an etiopathogenic role in anogenital LS, but the association is unclear.²⁰

Our LS patients had an increased risk of endometrial cancer, an association that has not been reported previously. Accordingly, the pathogenesis and development of LS may not be solely dermatologic, but may also be associated with metabolic and lifestyle factors. Hypertension, type 2 diabetes, and overweight are more common among the patients with LS,^{24,25} but older age, obesity, and diabetes are also risk factors for endometrial cancer and could explain the increased risk in LS patients. Menorrhagia and postmenopausal bleeding were combined because patients with different types of bleeding usually have to use sanitary towels for long periods, and the moist sanitary towels may cause irritation in vulvar mucosa. This could at least partly explain the association between menstrual disorders and LS.

Our findings were in discrepancy with a large register-based study, where the risk of cervical and endometrial cancers was not elevated in LS patients.¹⁰ The reason for this discrepancy is the difference in study methods: our study was a cross-sectional study, where the cancer might also have preceded the LS diagnosis. The

study of Halonen et al.¹⁰ was a register-based study, where they evaluated the incidence of the cancer diagnosis after LS diagnosis.

Infections of the vagina and vulva were also more common in the LS patients and were mainly chronic. It is possible that in inexperienced hands, LS patients might be misdiagnosed as having, for example, vulvitis. Lichen sclerosus presumably alters the regulation of the inflammatory system by an infectious etiologic of LS, as the disease itself, or as a consequence of LS treatment. In our study, 9 of our LS patients had ulcers in genital mucosa, although it is very rarely seen in LS. Our LS patients also showed a higher prevalence of dyspareunia, and chronic infection could especially contribute to this symptom. Hence, LS may cause sexual dysfunction.¹¹ Actually, women with LS reportedly have less frequent sexual activity and are less satisfied with sexual life.¹¹ Vulvar pain and symptoms, for any reason, may affect mental and physical health crucial for sexual health.²⁶

In agreement with previous studies,^{17,27} lower urinary tract symptoms were more common in our LS patients. Similar rates of lower urinary tract symptoms have been described in women with biopsy-proven LS and vulvar diseases without LS.¹⁷ In our study, the risk for interstitial cystitis was 5 times greater in the LS patients than in the control cohort, and the LS patients also experienced more urinary incontinence (stress and urgency incontinence). Chronic irritation from exposure to liquids, such as urine, may be the triggering factor.³ In general, OAB seems to be the most predominant type of lower urinary tract LS symptom.²⁷ Women with LS have been reported to have a higher prevalence of both OAB and urinary incontinence,¹⁷ but OAB was not more frequent in our LS patients. In our country, OAB symptoms without incontinence are predominantly diagnosed and treated in primary health care or private clinics. The diagnoses in the present study were collected only from our tertiary referral clinic and possibly reflected patients with more severe symptoms, which could have led to bias concerning the occurrence of OAB.

Previous studies have shown an association between LS and bowel comorbidities.¹⁴ In our study of gastrointestinal disorders associated with LS, the risk of celiac disease was notable. However, the risk for Crohn disease or ulcerative colitis in LS patients was not increased. An autoimmune association with vulvar LS has been demonstrated previously in many studies.^{1,28} However, a co-occurrence of celiac disease in LS has not been widely reported. One published study has shown a co-occurrence in pediatric patients with LS,¹³ whereas another is a case report of celiac disease in 1 woman with LS.¹⁸ Thus, celiac disease should be considered among other autoimmune diseases during follow-up of LS patients.

In agreement with previous studies, the risk of functional bowel disorders, such as constipation and diarrhea, was increased among the LS patients. We also found a greater prevalence of

diverticular disease of the intestine among our LS patients, likely a reflected consequence of constipation. In our study, the LS patients also had more anal fissuring and nonspecific gastrointestinal bleeding. These may represent manifestations of LS rather than being separate entities. Estimates of the frequency of gastrointestinal disorders vary widely,^{14,17} but constipation is a common symptom in pediatric LS patients. In children with LS, 89% have at least 1 gastrointestinal-related complaint (bleeding with bowel movements, fissuring, soiling fecal impaction, or constipation).²⁹

Our study had some limitations. Because in our study design, the diagnosis of LS was clinical, based on the guidelines of the European Dermatology Forum,³ some patients with negative histology could be also included in the study. Another limitation was that the data were collected from medical records, and the diagnosis was included only if it was entered with an ICD code. For example, ICD-10 code D07.1 certainly contains only dVIN diagnosis, but code N90.2 might include both vulvar HSIL and dVIN. Thus, we have no information regarding cases with diagnoses recorded as free text in the medical records, although the diagnosis of LS in our study was defined by a specialist in gynecology. We were unable to gather information on known confounders, including parity, body mass index, and smoking habits, which may have accounted for our findings. The present findings were based on prevalent LS cases with no follow-up data. The cross-sectional study design precluded determination of whether the comorbidities were diagnosed before or after the LS diagnosis. In the current analysis, the prevalence of LS was 1.8:1,000, in line with prevalence estimations in other publications.^{4,30} Thus, we assume that our dataset is a representative sample of LS in women and girls. Our results were verified in patients with biopsy-proven LS, which strengthens the study.

CONCLUSIONS

Our results indicate that LS patients are at risk for several comorbidities. Some of these may act as triggers for the development of LS, whereas others are clearly LS consequences, suggesting a complex pathophysiology for LS. Thus, LS-associated comorbidities may also have a significant effect on quality of life and should be considered when treating patients with LS.

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