Vulvar Lichen Sclerosus

Subjects: Dermatology

Contributor: Adelina Popa, Mihai Cristian Dumitrascu, Aida Petca, Razvan-Cosmin Petca, Florica Sandru

Vulvar lichen sclerosus (VLS) is a frequently overlooked inflammatory disorder affecting the skin and mucous membranes of the vulva. With a propensity for atrophy, severe scarring, functional impairment, and malignant evolution, VLS is a disease that recurs frequently; early diagnosis, rapid treatment, and ongoing patient follow-up are essential. Potent topical corticosteroids (TCSs) are now widely recognized as the most effective treatment for achieving remission in VLS, but considering the potential complications of long-term treatment with potent TCSs, understanding the evolution of VLS during puberty becomes particularly crucial in determining the necessity for aggressive or more conservative therapeutic interventions.

Keywords: vulvar lichen sclerosus ; puberty ; photodynamic therapy ; carbon dioxide laser ; clobetasol propionate

1. Introduction

Vulvar lichen sclerosus (VLS) is a frequently overlooked inflammatory disorder affecting the skin and mucous membranes of the vulva and was initially described in 1887 [1]. Since then, a number of synonyms have been used, including “guttate scleroderma”, “lichen sclerosus et atrophicus”, “white spot disease”, “vulvar dystrophy”, and “Kraurosis vulvae”. The word “lichen sclerosus”, now used for both genital and extragenital lesions, has superseded all of these other designations [1][2].

VLS produces chronic itching and pain in the vaginal area and the area surrounding the anus. Scarring following inflammation can cause serious harm by causing the clitoris to be buried in women and girls, the vulval lips (labia) to fuse, and the vaginal aperture to constrict; with a propensity for atrophy, severe scarring, functional impairment, and malignant evolution, VLS is a disease that recurs frequently [3][4]. Early diagnosis, rapid treatment, and ongoing patient follow-up are essential [5]. Spontaneous remissions rarely occur [4]. Although no cure for LS exists, it can be managed with proper care [4]. Early intervention can potentially avert long-term consequences such as anatomical structural deterioration and the development of squamous cell carcinoma (SCC) [6]. Controversies surrounding the pathogenesis of VLS have prompted extensive research, leading to the exploration of various treatment modalities.

2. Unraveling the Complexities: Exploring the Role of Sex Hormones in Vulvar Lichen Sclerosus

Due to the shortage of comprehensive epidemiologic screening studies in this field and a sizable portion of cases may be asymptomatic (15–40%), the actual prevalence of LS is unknown [7][8][9]. Previous research has revealed LS to be an uncommon illness that affects 1 in 300–1000 women [10]; nevertheless, more recent research indicates a greater frequency (1 in 60) [11], and it can potentially reach as high as 1 in 30 in older populations [12]. According to a research study conducted in the United States from 2015 to 2017, LS had a claims-based prevalence of 0.05%, which is lower than previously reported and shows considerable underdiagnosis [13]. Although VLS affects women of all ages, its prevalence peaks at two different ages: prepubertal girls (1 in 900) and peri- or post-menopausal women (i.e., after menopause) [14] [15]. These peaks support the idea that hypoestrogenism plays a role in the development of VLS. The first peak is expected to comprise 7–15% of all cases [16]. Nevertheless, not all authors find it consistent [7][11]. The range of the mean age at diagnosis is 52.6 to 60 years old [7][11][17][18][19]; however, the length of time symptoms can last before that can be substantial (68 ± 11.2 months) [7], raising doubts about the actual role of menopause in the disease’s development.

A possible explanation for its genesis is the vulva’s decreased level of the enzyme 5α-reductase. In a study, 30 women with untreated VLS had their serum hormone levels (estradiol, testosterone, dihydrotestosterone, androstenedione, and sex hormone-binding globulin) measured. Patients with untreated VLS had significantly higher levels of free testosterone and considerably lower levels of dihydrotestosterone and androstenedione in their serum when compared to typical values for their age [20]. Additionally, a number of studies have shown that VLS has fewer nuclear androgen receptors and that well-developed VLS has fewer androgen receptors than early VLS [21][22][23]. As proposed by Clifton et al., the loss of

androgen receptor expression (down-regulation) in VLS may be secondary, resulting from a change in the squamous phenotype rather than a hormonal etiology [21].

The change from vaginal to vulva genitalia in a normal female is characterized by an increase in androgen receptors and a decrease in estrogen and progesterone receptors. A subset of LS patients appears to have lower vulvar androgen receptor expression [21][22]. Recent research indicates that oral contraceptive pills, particularly those with antiandrogenic qualities, may disrupt the androgen-dependent growth of the vulvar skin, thereby causing the early onset of LS in a minority of sensitive young women [24][25].

3. Interplay of Autoimmunity and Genetics in VLS

Research has documented a significant prevalence of autoimmune disease in individuals with VLS, along with much greater levels of autoantibody detection; however, it is essential to note that this does not definitively establish VLS as an autoimmune condition [26][27]. A critical complicating element is that middle-aged female patients, who make up the primary group affected by this disorder, exhibit a considerably elevated prevalence of autoantibodies [27]. A meticulously conducted study revealed that individuals with VLS experience autoimmune disease at a higher frequency compared to individuals of the same age who do not have VLS; approximately 30% of VLS patients are affected by autoimmune disease, whereas the prevalence in the general population is 10%. In addition, about 30% of individuals had a favorable familial background. Nevertheless, the investigation revealed no notable disparity in the rate of autoantibody detection between individuals with VLS and the control group. The two disorders most frequently observed in conjunction were autoimmune thyroid disease and vitiligo [28]. Furthermore, VLS has been associated with morphea, alopecia areata, and pernicious anemia [29][30]. There have been reports of diabetes, psoriasis, and celiac disease co-existing; however, this may be a coincidence [31][32][33].

A frequently cited study found that 67% of the 30 patients with LS in the group had serum immunoglobulin G (IgG) antibodies to ECM-1, while only 7% of the control group had these antibodies [34]. The study, regrettably, has not provided us with any additional understanding of the etiology. Nevertheless, it does reinforce the assumption that VLS is an autoimmune disorder, even if this hypothesis has not been verified [34][35]. Encountering a low-titer positive antinuclear antibody (ANA) is not unusual, although it is seldom important enough to justify more research [36]. If thyroid autoantibodies are detected, additional examination is necessary [37][38]. Despite the existence of thyroid autoantibodies, thyroid function can remain within the normal parameters [38][39].

Familial occurrence of LS is observed; however, it is predominantly attributed to random chance [40][41]. Consequently, there has been a quest to identify a correlation between human leukocyte antigen (HLA) and the situation [40]. While there have been no observed associations with the autoimmune-related HLA antigens HLA A1, B8, and DR3, the HLA class II antigens HLA-DQ7, HLA-DR11, and HLA-DR12 have the highest susceptibility to LS [42]. Although the confirmed HLA connections are intriguing, insufficient substantial data can definitively evaluate these associations' strength [43].

Epigenetic modifications can lead to functional deficits in the genome unrelated to the DNA sequence. These modifications can result in modified gene expression and phenotypic alterations. A recent study has discovered changes in the enzyme expression in VLS caused by an epigenetic alteration. This finding suggests that there may be an epigenetic basis for developing the disease [44].

4. VLS: Current Treatment Paradigm

Potent topical corticosteroids (TCSs) are now widely recognized as the most effective treatment for remission in VLS [45] [46]. The initial documentation of this therapy was released in 1991, utilizing clobetasol propionate (CP) 0.05%, a powerful TCS [47]. Subsequently, numerous further reports were published [48][49][50]. Prior to the publication of that article [47], it was deemed inconceivable to administer potent TCSs to the skin of the genitals. Instead, treatment protocols involved the administration of mild TCSs, as well as testosterone and progesterone; consequently, VLS was deemed highly challenging to cure [51][52].

Studies and publications commonly indicate that the problem cannot be resolved independently and requires management. However, there is no agreement on the specific methods for long-term treatment of the condition [53][54][55]. The release of a recent guideline acknowledged that treatment for women is still inadequate, as scar development, which can cause disability, is a common occurrence despite treatment. According to the same evaluation, the treatment primarily focuses on reducing symptoms, and proactive management may be considered to sustain remission in cases of active disease. Still, no explicit suggestion was provided [54].

Tacrolimus and pimecrolimus, topical immunosuppressive medications, may treat VLS in children and adults [47][56][57][58]. In a phase II trial from 2006, tacrolimus ointment 0.1% was tested for VLS patients; at 24 weeks, 43% of patients had total active LS resolution and 34% had partial resolution [59]. Topical immunosuppressive medicines may increase the risk of malignant transformation, even though no adverse events occurred throughout the 18-month monitoring period. Pimecrolimus therapy can cause SCC in VLS patients [60].

Topical tretinoin has been utilized as the sole treatment for VLS. Still, insufficient evidence supports its effectiveness, and it may be restricted due to its potential to cause irritation [61].

Phototherapy (narrowband UVB, UVA1, and topical PUVA phototherapy) [62][63][64] for VLS should only be considered after traditional therapies have proven ineffective, as it does not offer superior symptom alleviation, quality of life improvement, or practicality compared to TCSs [65]. In addition, the occurrence of skin cancer following phototherapy can be problematic in the genital areas, especially considering the heightened risk of cancer in VLS [66]. Photodynamic therapy (PDT) using topical 5-aminolevulinic acid (5-ALA) is a viable treatment option for uncontrollable itching in VLS when other treatments have been unsuccessful [65]. Nevertheless, there is disagreement regarding the clinical and histological improvements [67]. Some instances showed healing of superficial erosions and improvement of clinical symptoms after PDT, while others did not show any clinical changes [68][69]. However, other researchers have reported an increased occurrence of apoptosis and the eradication of persistent inflammation [70][71]. Surgery for women with anogenital LS should only be considered for patients who have vulvar intraepithelial neoplasia or malignancy or for those who need correction of scarring that is affecting normal function. Introital stenosis can cause problems with urination or sexual intercourse and may necessitate introital widening. It is advisable to postpone surgery until the disease activity has subsided [1].

References

1. Fistarol, S.K.; Itin, P.H. Diagnosis and treatment of lichen sclerosus: An update. Am. J. Clin. Dermatol. 2013, 14, 27–47.
2. Fergus, K.B.; Lee, A.W.; Baradaran, N.; Cohen, A.J.; Stohr, B.A.; Erickson, B.A.; Mmonu, N.A.; Breyer, B.N. Pathophysiology, Clinical Manifestations, and Treatment of Lichen Sclerosus: A Systematic Review. Urology 2020, 135, 11–19.
3. Krapf, J.M.; Mitchell, L.; Holton, M.A.; Goldstein, A.T. Vulvar Lichen Sclerosus: Current Perspectives. Int. J. Women's Health 2020, 12, 11–20.
4. Pope, R.; Lee, M.H.; Myers, A.; Song, J.; Abou Ghayda, R.; Kim, J.Y.; Hong, S.H.; Lee, S.B.; Koyanagi, A.; Jacob, L.; et al. Lichen Sclerosus and Sexual Dysfunction: A Systematic Review and Meta-Analysis. J. Sex. Med. 2022, 19, 1616–1624.
5. Gautam, M.M.; Singh, V.; Nadkarni, N.J.; Patil, S.P. Anogenital lichen sclerosus. Indian J. Sex. Transm. Dis. 2020, 41, 1–9.
6. Moyal-Barracco, M.; Wendling, J. Vulvar dermatosis. Best Pract. Res. Clin. Obstet. Gynaecol. 2014, 28, 946–958.
7. Vieira-Baptista, P.; Lima-Silva, J.; Cavaco-Gomes, J.; Beires, J.; Martinez-de-Oliveira, J. What differentiates symptomatic from asymptomatic women with lichen sclerosus? Gynecol. Obstet. Investig. 2015, 79, 263–268.
8. Tran, D.A.; Tan, X.; Macri, C.J.; Goldstein, A.T.; Fu, S.W. Lichen Sclerosus: An autoimmunopathogenic and genomic enigma with emerging genetic and immune targets. Int. J. Biol. Sci. 2019, 15, 1429–1439.
9. Singh, N.; Ghatage, P. Etiology, Clinical Features, and Diagnosis of Vulvar Lichen Sclerosus: A Scoping Review. Obstet. Gynecol. Int. 2020, 2020, 7480754.
10. Tremaine, R.D.; Miller, R.A. Lichen sclerosus et atrophicus. Int. J. Dermatol. 1989, 28, 10–16.
11. Goldstein, A.T.; Marinoff, S.C.; Christopher, K.; Srodon, M. Prevalence of vulvar lichen sclerosus in a general gynecology practice. J. Reprod Med. 2005, 50, 477–480.
12. Leibovitz, A.; Kaplun, V.V.; Saposhnicov, N.; Habot, B. Vulvovaginal examinations in elderly nursing home women residents. Arch. Gerontol. Geriatr. 2000, 31, 1–4.
13. Melnick, L.E.; Steuer, A.B.; Bieber, A.K.; Wong, P.W.; Pomeranz, M.K. Lichen sclerosus among women in the United States. Int. J. Women's Dermatol. 2020, 6, 260–262.
14. Powell, J.; Wojnarowska, F. Childhood vulvar lichen sclerosus: An increasingly common problem. J. Am. Acad. Dermatol. 2001, 44, 803–806.
15. Neill, S.M.; Tatnall, F.M.; Cox, N.H. British Association of Dermatologists. Guidelines for the management of lichen sclerosus. Br. J. Dermatol. 2002, 147, 640–649.

16. Powell, J.J.; Wojnarowska, F. Lichen sclerosus. Lancet 1999, 353, 1777–1783.
17. Bleeker, M.C.; Visser, P.J.; Overbeek, L.I.; van Beurden, M.; Berkhof, J. Lichen Sclerosus: Incidence and Risk of Vulvar Squamous Cell Carcinoma. Cancer Epidemiol. Biomarkers Prev. 2016, 25, 1224–1230.
18. Micheletti, L.; Preti, M.; Radici, G.; Boveri, S.; Di Pumpo, O.; Privitera, S.S.; Ghiringhello, B.; Benedetto, C. Vulvar Lichen Sclerosus and Neoplastic Transformation: A Retrospective Study of 976 Cases. J. Low. Genit. Tract Dis. 2016, 20, 180–183.
19. Lee, A.; Bradford, J.; Fischer, G. Long-term Management of Adult Vulvar Lichen Sclerosus: A Prospective Cohort Study of 507 Women. JAMA Dermatol. 2015, 151, 1061–1067.
20. Friedrich EGJr Kalra, P.S. Serum levels of sex hormones in vulvar lichen sclerosus, and the effect of topical testosterone. N. Engl. J. Med. 1984, 310, 488–491.
21. Clifton, M.M.; Garner, I.B.; Kohler, S.; Smoller, B.R. Immunohistochemical evaluation of androgen receptors in genital and extragenital lichen sclerosus: Evidence for loss of androgen receptors in lesional epidermis. J. Am. Acad. Dermatol. 1999, 41, 43–46.
22. Hodgins, M.B.; Spike, R.C.; Mackie, R.M.; MacLean, A.B. An immunohistochemical study of androgen, oestrogen and progesterone receptors in the vulva and vagina. Br. J. Obstet. Gynaecol. 1998, 105, 216–222.
23. Carlson, J.A.; Murphy, M. Androgen receptors and lichen sclerosus. J. Am. Acad. Dermatol. 2000, 43, 559–560.
24. Günthert, A.R.; Faber, M.; Knappe, G.; Hellriegel, S.; Emons, G. Early onset vulvar Lichen Sclerosus in premenopausal women and oral contraceptives. Eur. J. Obstet. Gynecol. Reprod. Biol. 2008, 137, 56–60.
25. Murphy, R. Lichen sclerosus. Dermatol. Clin. 2010, 28, 707–715.
26. Oyama, N.; Hasegawa, M. Lichen Sclerosus: A Current Landscape of Autoimmune and Genetic Interplay. Diagnostics 2022, 12, 3070.
27. Lee, A.; Fischer, G. Diagnosis and Treatment of Vulvar Lichen Sclerosus: An Update for Dermatologists. Am. J. Clin. Dermatol. 2018, 19, 695–706.
28. Cooper, S.M.; 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.
29. Harrington, C.I.; Dunsmore, I.R. An investigation into the incidence of auto-immune disorders in patients with lichen sclerosus and atrophicus. Br. J. Dermatol. 1981, 104, 563–566.
30. Kyriakis, K.P.; Emmanuelides, S.; Terzoudi, S.; Palamaras, I.; Damoulaki, E.; Evangelou, G. Gender and age prevalence distributions of morphea en plaque and anogenital lichen sclerosus. J. Eur. Acad. Dermatol. Venereol. 2007, 21, 825–826.
31. Jacobs, L.; Gilliam, A.; Khavari, N.; Bass, D. Association between lichen sclerosus and celiac disease: A report of three pediatric cases. Pediatr. Dermatol. 2014, 31, e128–e131.
32. Hofer, M.D.; Meeks, J.J.; Mehdiratta, N.; Granieri, M.A.; Cashy, J.; Gonzalez, C.M. Lichen sclerosus in men is associated with elevated body mass index, diabetes mellitus, coronary artery disease and smoking. World J. Urol. 2014, 32, 105–108.
33. Simpkin, S.; Oakley, A. Clinical review of 202 patients with vulval lichen sclerosus: A possible association with psoriasis. Australas. J. Dermatol. 2007, 48, 28–31.
34. Oyama, N.; Chan, I.; Neill, S.M.; Hamada, T.; South, A.P.; Wessagowit, V.; Wojnarowska, F.; D'Cruz, D.; Hughes, G.J.; Black, M.M.; et al. Autoantibodies to extracellular matrix protein 1 in lichen sclerosus. Lancet 2003, 362, 118–123.
35. Hamada, T.; Wessagowit, V.; South, A.P.; Ashton, G.H.; Chan, I.; Oyama, N.; Siriwattana, A.; Jewhasuchin, P.; Charuwichitratana, S.; Thappa, D.M.; et al. Extracellular matrix protein 1 gene (ECM1) mutations in lipoid proteinosis and genotype-phenotype correlation. J. Investig. Dermatol. 2003, 120, 345–350.
36. Regauer, S. Immune dysregulation in lichen sclerosus. Eur. J. Cell Biol. 2005, 84, 273–277.
37. Wright, A.J. Lichen sclerosus thyroid disease. J. Reprod. Med. 1998, 43, 240.
38. Birenbaum, D.L.; Young, R.C. High prevalence of thyroid disease in patients with lichen sclerosus. J. Reprod. Med. 2007, 52, 28–30.
39. Lynch, P.J. Lichen sclerosus and thyroid disease. J. Reprod. Med. 1999, 44, 315–316.
40. De Luca, D.A.; Papara, C.; Vorobyev, A.; Staiger, H.; Bieber, K.; Thaçi, D.; Ludwig, R.J. Lichen sclerosus: The 2023 update. Front. Med. 2023, 10, 1106318.

41. Marren, P.; Yell, J.; Charnock, F.M.; Bunce, M.; Welsh, K.; Wojnarowska, F. The association between lichen sclerosus and antigens of the HLA system. Br. J. Dermatol. 1995, 132, 197–203.
42. Yang, M.; Sun, K.; Chang, J. Screening differential circular RNAs expression profiles in Vulvar Lichen Sclerosus. Biomed. Eng. Online 2022, 21, 51.
43. Aslanian, F.M.; Marques, M.T.; Matos, H.J.; Pontes, L.F.; Porto, L.C.; Azevedo, L.M.; Filgueira, A.L. HLA markers in familial Lichen sclerosus. J. Dtsch. Dermatol. Ges. 2006, 4, 842–847, (In English, Germany).
44. Gambichler, T.; Terras, S.; Kreuter, A.; Skrygan, M. Altered global methylation and hydroxymethylation status in vulvar lichen sclerosus: Further support for epigenetic mechanisms. Br. J. Dermatol. 2014, 170, 687–693.
45. Lewis, F.M.; Tatnall, F.M.; Velangi, S.S.; Bunker, C.B.; Kumar, A.; Brackenbury, F.; Mohd Mustapa, M.F.; Exton, L.S. British Association of Dermatologists guidelines for the management of lichen sclerosus, 2018. Br. J. Dermatol. 2018, 178, 839–853.
46. van der Meijden, W.I.; Boffa, M.J.; Ter Harmsel, W.A.; Kirtschig, G.; Lewis, F.M.; Moyal-Barracco, M.; Tiplica, G.S.; Sherrard, J. 2016 European guideline for the management of vulval conditions. J. Eur. Acad. Dermatol. Venereol. 2017, 31, 925–941.
47. Dalziel, K.L.; Millard, P.R.; Wojnarowska, F. The treatment of vulval lichen sclerosus with a very potent topical steroid (clobetasol propionate 0.05%) cream. Br. J. Dermatol. 1991, 124, 461–464.
48. Renaud-Vilmer, C.; Cavelier-Balloy, B.; Porcher, R.; Dubertret, L. Vulvar lichen sclerosus: Effect of long-term topical application of a potent steroid on the course of the disease. Arch. Dermatol. 2004, 140, 709–712.
49. Bradford, J.; Fischer, G. Long-term management of vulval lichen sclerosus in adult women. Aust. N. Z. J. Obstet. Gynaecol. 2010, 50, 148–152.
50. Corazza, M.; Borghi, A.; Minghetti, S.; Toni, G.; Virgili, A. Clobetasol propionate vs. mometasone furoate in 1-year proactive maintenance therapy of vulvar lichen sclerosus: Results from a comparative trial. J. Eur. Acad. Dermatol. Venereol. 2016, 30, 956–961.
51. Ayhan, A.; Urman, B.; Yüce, K.; Ayhan, A.; Gököz, A. Topical testosterone for lichen sclerosus. Int. J. Gynaecol. Obstet. 1989, 30, 253–255.
52. Ayhan, A.; Yüce, K.; Urman, B.; Ayhan, A.; Gököz, A. Vulvar dystrophies: An evaluation. Aust. N. Z. J. Obstet. Gynaecol. 1989, 29 Pt 1, 250–252.
53. Funaro, D. Lichen sclerosus: A review and practical approach. Dermatol. Ther. 2004, 17, 28–37.
54. Tasker, G.L.; Wojnarowska, F. Lichen sclerosus. Clin. Exp. Dermatol. 2003, 28, 128–133.
55. Val, I.; Almeida, G. An overview of lichen sclerosus. Clin. Obstet. Gynecol. 2005, 48, 808–817.
56. Kirtschig, G.; Cooper, S.; Aberer, W.; Günthert, A.; Becker, K.; Jasaitiene, D.; Chi, C.C.; Kreuter, A.; Rall, K.; Riechardt, S.; et al. Evidence-based (S3) Guideline on (anogenital) Lichen sclerosus. J. Eur. Acad. Dermatol. Venereol. 2017, 31, e81–e83.
57. Luqman, T.S.; Kalavant, A.; Sunil Kumar, K.S.; Swathy, A.R. Vulvar Lichen Sclerosus Et Atrophicus: Refractory to Standard Therapy. J. Indian Assoc. Pediatr. Surg. 2023, 28, 345–347.
58. Funaro, D.; Lovett, A.; Leroux, N.; Powell, J. A double-blind, randomized prospective study evaluating topical clobetasol propionate 0.05% versus topical tacrolimus 0.1% in patients with vulvar lichen sclerosus. J. Am. Acad. Dermatol. 2014, 71, 84–91.
59. Hengge, U.R.; Krause, W.; Hofmann, H.; Stadler, R.; Gross, G.; Meurer, M.; Brinkmeier, T.; Frosch, P.; Moll, I.; Fritsch, P.; et al. Multicentre, phase II trial on the safety and efficacy of topical tacrolimus ointment for the treatment of lichen sclerosus. Br. J. Dermatol. 2006, 155, 1021–1028.
60. Fischer, G.; Bradford, J. Topical immunosuppressants, genital lichen sclerosus and the risk of squamous cell carcinoma: A case report. J. Reprod. Med. 2007, 52, 329–331.
61. Borghi, A.; Corazza, M.; Minghetti, S.; Virgili, A. Topical tretinoin in the treatment of vulvar lichen sclerosus: An advisable option? Eur. J. Dermatol. 2015, 25, 404–409.
62. Garrido-Colmenero, C.; Martínez-Peinado, C.M.; Galán-Gutiérrez, M.; Barranco-Millán, V.; Ruiz-Villaverde, R. Successful response of vulvar lichen sclerosus with NB-UVB. Dermatol. Ther. 2021, 34, e14801.
63. Reichrath, J.; Reinhold, U.; Tilgen, W. Treatment of genito-anal lesions in inflammatory skin diseases with PUVA cream photochemotherapy: An open pilot study in 12 patients. Dermatology 2002, 205, 245–248.
64. Rombold, S.; Lobisch, K.; Katzer, K.; Grazziotin, T.C.; Ring, J.; Eberlein, B. Efficacy of UVA1 phototherapy in 230 patients with various skin diseases. Photodermatol. Photoimmunol. Photomed. 2008, 24, 19–23.

65. Terras, S.; Gambichler, T.; Moritz, R.K.; Stücker, M.; Kreuter, A. UV-A1 phototherapy vs clobetasol propionate, 0.05%, in the treatment of vulvar lichen sclerosus: A randomized clinical trial. JAMA Dermatol. 2014, 150, 621–627.
66. Kirtschig, G.; Becker, K.; Günthert, A.; Jasaitiene, D.; Cooper, S.; Chi, C.C.; Kreuter, A.; Rall, K.K.; Aberer, W.; Riechardt, S.; et al. Evidence-based (S3) Guideline on (anogenital) Lichen sclerosus. J. Eur. Acad. Dermatol. Venereol. 2015, 29, e1–e43.
67. Gerkowicz, A.; Szczepanik-Kułak, P.; Krasowska, D. Photodynamic Therapy in the Treatment of Vulvar Lichen Sclerosus: A Systematic Review of the Literature. J. Clin. Med. 2021, 10, 5491.
68. Wang, Y.; Hao, J.; Liu, J. High-frequency ultrasound assessment of vulvar lichen sclerosus treated with photodynamic therapy. Photodiagnosis Photodyn. Ther. 2023, 41, 103277.
69. Zhang, F.; Li, D.; Shi, L.; Gu, Y.; Xu, Y. 5-ALA-photodynamic therapy in refractory vulvar lichen sclerosus et atrophicus. Int. J. Clin. Exp. Pathol. 2020, 13, 3100–3110.
70. Declercq, A.; Güvenç, C.; De Haes, P. Proposition of standardized protocol for photodynamic therapy for vulvar lichen sclerosus. J. Dermatol. Treat. 2022, 33, 560–568.
71. Zawislak, A.A.; McCluggage, W.G.; Donnelly, R.F.; Maxwell, P.; Price, J.H.; Dobbs, S.P.; McClelland, H.R.; Woolfson, A.D.; Mccarron, P.A. Response of vulval lichen sclerosus and squamous hyperplasia to photodynamic treatment using sustained topical delivery of aminolevulinic acid from a novel bioadhesive patch system. Photodermatol. Photoimmunol. Photomed. 2009, 25, 111–113.