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Major clinical, nutrological and immunological considerations and treatments of vulvar lichen sclerosus: an integrative systematic review

Maria Claudia Tessari Ferreira[1*], Fabíola Soares Moreira Campos[2], Ilka Lopes Santoro[3]

[1] UNIVÁS - University of the Sapucaí Valley, Pouso Alegre, Minas Gerais, Brazil.
[2] Department of Gynecology and Obstetrics, UNIVÁS - University of the Sapucaí Valley, Pouso Alegre, Minas Gerais, Brazil.
[3] UNIFESP - Federal University of São Paulo, São Paulo, Brazil.

*Corresponding author: Maria Claudia Tessari Ferreira.
UNIVÁS - University of the Sapucaí Valley, Pouso Alegre,
Minas Gerais, Brazil.
E-mail: caltessari@hotmail.com

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Abstract

Introduction: Vulvar Lichen Sclerosus (VLS) is characterized by being a chronic progressive inflammatory skin disease, mediated by lymphocytes, which mainly affects the anogenital area. Its prevalence is higher in the female population (10:1), especially in postmenopausal women, and is associated with autoimmune diseases, although it can affect both sexes. It is one of the diseases that most causes structural damage to the vulva and consequent physical and mental suffering. The diagnosis of vulvar lichen sclerosus is clinical. Biopsy is indicated only in cases of non-typical lesions. **Objective:** This was to conduct an integrative systematic review to present the main clinical, nutrological, and immunological considerations of vulvar lichen sclerosus, as well as the treatment challenges. **Methods:** The systematic review rules of the PRISMA Platform were followed. The search was conducted from September to October 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 112 articles were found. 38 articles were fully evaluated and 22 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 32 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=90.7%>50%. It was concluded that the exact cause of VLS is not fully understood. Still, it is believed that nutritional factors, dysbiosis of the intestinal microbiota, genetics, autoimmunity, and hormonal imbalance may play an important role in its development. The main risk factor for vulvar cancer associated with VLS is delayed diagnosis, so controlling symptoms and preventing complications is crucial, and regular follow-up is necessary to monitor response to treatment and disease recurrence.

Keywords: Vulvar lichen sclerosus. Nutrology. Immunity. Gut microbiota. Treatments.

Introduction

Lichen is a disease-causing fungus that can affect different regions of the body. However, when the vulvar area is the dominant involvement, this entity can be classified into three types: simple, flat, and sclerotic, the latter being the subject of this review **[1]**. Less recognized are the variants of Vulvar Lichen Sclerosus (VLS), which comprise two subtypes: vestibular sclerosis and the non-sclerotic form **[2]**.

The vestibular sclerosis variant is the VLS variant in which localized involvement of the anterior vestibule is observed, and among the histopathological characteristics of this variant is the absence or presence of a rare lymphocytic infiltrate **[3]**. In the second variant, the non-sclerotic form, the clinical findings are compatible, but it does not exhibit sclerosis of the dermis, therefore requiring clinical-pathological correlation to establish the diagnosis. It is important to

note that four subtypes of the non-sclerotic variant have been described, including lichenoid, hypertrophic lichenoid, dermal fibrosis without acanthosis, and dermal fibrosis with acanthosis **[2,4]**.

VLS is characterized as a chronic progressive inflammatory skin disease, mediated by lymphocytes **[5]**, which mainly affects the anogenital area. The predominantly affected sites are the interlabial sulcus, labia majora and minora, clitoris, and clitoral horn. If there is an extension to the perineal or perianal region, a figure of eight will be formed. The vagina is usually spared. Although it is an entity of unknown cause, there is a positive association with the presence of autoimmune diseases and estrogen deficiency **[1,2]**.

Also, VLS prevalence is higher in the female population (10:1), but it can affect both sexes **[1,6]**. It has a bimodal presentation and an estimated incidence of 0.1 and 3% in the pre-puperal and postmenopausal phases, respectively **[1,5,6]**. It is believed that the prevalence may be underestimated since 30% of cases are in asymptomatic individuals. Still, it is estimated that it varies from 1:60 to 1:1000. VLS is one of the diseases that most cause structural damage to the vulva and consequently physical and mental suffering **[1,5]**.

The main symptoms are intense itching, burning in the vulvar region, and dyspareunia, caused by anatomical changes, and the presence of erosions, fissures, and scars **[1,5]**. In a more advanced stage, the disease presents as ulcerative lesions on the vulva, often hemorrhagic, reduction of the labia minora, narrowing of the vaginal introitus, urinary retention, anal stenosis, and intestinal constipation, which causes great discomfort not only physically but also emotionally, resulting in significant impairment of quality of life and well-being **[5,7]**.

Measuring the burden of VLS as a disease and treatment is challenging. Although there is still no standard scale, in recent years several scales have been developed to measure progression, response, and the impact of the disease and its complications on quality of life. Evidence shows that after a diagnosis of VLS is established, these women are twice as likely to develop anxiety and/or depression. Hence the importance of disseminating knowledge about vulvar anatomy to the general population and demystifying the disease, so that it is not taboo or kept secret, to avoid stigma or prejudice **[2,7]**.

Furthermore, neglecting VLS implies the maintenance of a premalignant status or even progression to squamous cell carcinoma **[5]**, since this association is well established. It is estimated that the increased risk of squamous cell carcinoma is between 2-5%, and it is known that up to 80% of vulvar carcinomas arise in VLS lesions **[1,8]**.

The association of VLS with other autoimmune conditions, including thyroid disease and bullous pemphigus, is well established, and an association has been observed with psoriasis, high body mass index, use of statins, cholecystectomy, gynecological pain syndrome, interstitial cystitis, urinary incontinence, and celiac disease. An increase in VLS has been found, to as an adverse effect, in patients using targeted therapy for cancer treatment **[2]**.

The macroscopic appearance of VLS is a flat lesion, ivory or porcelain in color, with white spots that may coalesce into thin, pale, wrinkled plaques. Due to the presence of itching, it may present excoriation, erythema, and ecchymosis. Less frequently, hyperkeratosis occurs. The presence of progressive post-inflammatory scarring may cause irreversible subversion of the anogenital architecture, including fusion or loss of the labia minora, narrowing of the vaginal introitus, and coverage of the clitoris. Once again, the need for early identification and diagnosis of this entity, with subsequent treatment, is emphasized, thus avoiding the mutilating complications of the disease, although delayed diagnosis is frequent **[1,6,9]**.

The diagnosis of vulvar lichen sclerosus is clinical. A biopsy is indicated only in cases of non-typical lesions, suspected neoplasia, resistance to appropriate treatment, areas of hyperkeratosis and erosions that do not regress with treatment, or atypical extragenital presentation or altered pigmentation **[5]**. Typical pathological findings are orthokeratosis, loss or atrophy of the epidermis, degeneration of basal cells, hyalinization of the dermis with a homogenized band of dense fibrosis in the papillary dermis, accompanied by lymphocytic infiltrate **[1,4]**.

Naswa and Marfatia created a clinical score based on the signs and symptoms of the disease. This score consists of three grades described as follows: Grade I - no change or normal; Grade II - moderate; Grade III - severe. This classification helps in early diagnosis and appropriate treatment at the right time, thus avoiding undesirable complications **[6,10]**. The main differential diagnoses are: lichen planus, lichen simplex chronicus, vitiligo, and bulbar immune disease, such as mucous membrane pemphigoid, extramammary Paget's disease, and vulvar epithelial neoplasia **[1,4,6]**. Imaging studies are indicated in cases of urinary obstruction. The possibility of coexisting infection should be ruled out by microscopy or culture studies **[6]**.

Given this, the present study carried out an integrative systematic review to present the main clinical, nutrological, and immunological considerations of vulvar lichen sclerosus, as well as the treatment challenges.

Methods

Study Design

The present study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 10/19/2024. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 10/19/2024.

Research Strategy and Sources

The literature search process was carried out from September to October 2024 and developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following health science descriptors (DeCS/MeSH Terms) were used: "Vulvar lichen sclerosus. Nutrology. Immunity. Gut microbiota. Treatments", and using the Boolean "and" between the MeSH terms and "or" between the historical discoveries.

Study Quality and Risk of Bias

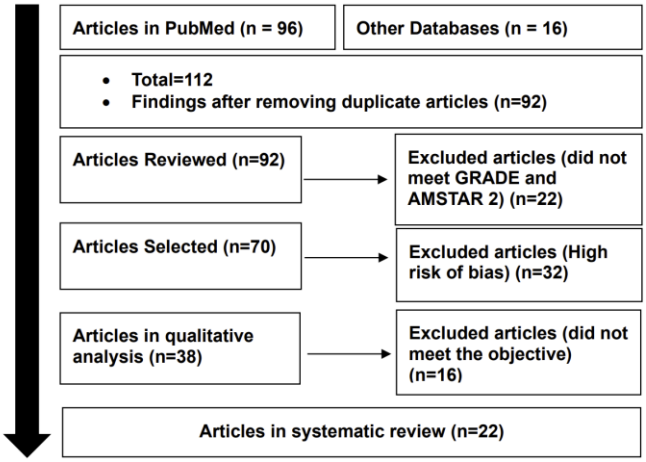
The quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of the analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and Discussion

Summary of Findings

A total of 112 articles were found that were submitted to eligibility analysis, and 22 final studies were selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=90.7%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 32 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2.

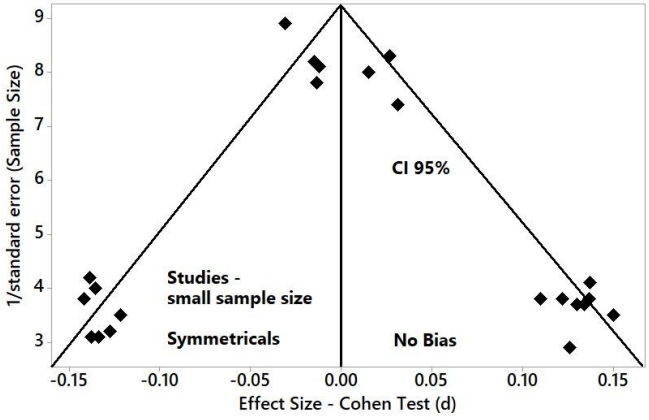
Figure 1. Flowchart showing the article selection process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. Studies with high confidence and high recommendation are shown above the graph (n=22 studies).



Source: Own authorship.

Main Treatment Considerations and Challenges - VLS (N=22 Studies)

The etiology and pathogenesis of Vulvar Lichen Sclerosus (VLS) is not a consensus in the literature. Current evidence indicates two main mechanisms: immune system imbalance and chronic inflammation **[1,5]**. The genetic association of VLS has been

demonstrated through studies involving family groups and twins **[4]**. Around 12% of more than a thousand women with VLS have at least one firstdegree relative with the same condition **[11]**.

Although familial predisposition is implicated in the development of VLS, as with any multifactorial disease, genetic and epigenetic predisposition reflect the cumulative effect of variations and expressions in the sequences of multiple loci, which VLS a susceptibility to the disease, the latter requiring interaction with exogenous factors for the disease to establish itself. An increased prevalence of some genes regulating antigens DQ7, DQ-8, DQ9, and DR12 was found compared to the control group. It was observed that among VLS carriers, 50% of adults and 66% of pre-puerperal women expressed HLA-DQ-7 class II HLA **[1,6,11]**. In contrast, HLA-DR-17 has a probable protective effect **[11]**.

Several agents are being studied, both in the skin and the blood of patients with EVL, and which could supposedly be involved in the development of the disease in predisposed individuals:

- VLS is not contagious, but bacteria and viruses seem to be involved in its etiology **[6]**. Infectious agents, such as Borrelia burgdorferi (Lyme disease), human papillomavirus (HPV), hepatitis C virus and Epstein-Barr virus may be involved in some way, but no results have been conclusive to date **[1,4,6]**.
- The skin microbiota comprises a complex microsystem, composed of millions of bacteria, fungi, and viruses in a state of dynamic equilibrium. Knowledge of the healthy microbiome is of fundamental importance because it can even influence carcinogenesis through the deregulation of inflammation, the immune system, and metabolism **[1,12,13]**. The composition of the microbial community is modulated by the physiological state of the skin, so the number or relative proportion of bacteria changes depending on endogenous and exogenous factors, humidity, and the presence of mucus **[14]**.

There is no consensus in the world literature regarding the bacterial composition of the vulva, so it is an area of great interest to researchers and major advances are expected in the coming years. It is known that there is great intra and interindividual variability, and since it is the gateway to the reproductive tract and is continuous with the vagina, the composition of the vulvar flora is influenced by the vaginal flora **[8,12,14,15]**.

Some studies have observed the presence of several genera including Lactobacilli, Corynebacteria, Staphylococci, and Prevotella, which suggests similarities with the corresponding vaginal environment associated with skin and intestinal commensals **[8,12,16,17]**. The microbiota can secrete an extracellular matrix, called biofilm, which adheres to the mucosal surface, and Lactobacilli, the most common microorganism, can grow in this environment, neutralizing and inhibiting toxin production, invasion, or adhesion of virulent hosts **[16]**.

Furthermore, dysbiosis was observed in the vulva, skin, and intestinal microbiota in VLS carriers, indicating the presence of an inflammatory process modulated by the immune system, thus there is a depletion of lactobacilli and an increase in Prevotella **[8]**. Thus, bacteria of the genus Prevotella, Peptostrepococcus, Porphyromonas, and Parimonas were found more frequently in the skin of girls with lichen compared to normal skin. In addition, Dialister, Clostridiales, Paraprevotella, *Escherichia coli*, *Bifidobacterium adolescentis*, and *Akkermansia muciniphila* were more frequent in intestinal microbiota samples from patients with lichen **[18,19]**.

A Danish case-control study demonstrated that the microbiota in the urine, upper and lower vagina, or intestine were specific and less diverse in patients with VLS when compared to the control, with a relative increase in the presence of streptococci, which suggests a possible relationship with the etiopathogenesis of the disease **[20]**. Another aspect to be highlighted is the regulated and mutualistic interrelationship between the vaginal, urethral, and intestinal microbiota **[1,16,18]** that suffer the combined effect of diet.

Thus, high-fat diets can reduce the dominance of lactobacilli, while a diet rich in sugar increases the growth of candida. On the other hand, emotional stress can suppress the cell-mediated immune response, which favors the relative growth of candida albicans. This set of factors can result in dysbiosis **[16]**. Gaining knowledge of the vulvar microbiome and its interrelation with VLS, through metabolomics and transcriptomics, may provide other possibilities for the design of new treatments for VLS **[12,14]**.

Also, trauma and chronic irritation are considered not only triggering agents but also factors that maintain the disease. Thus, mechanical elements such as tight clothing, occlusion, sexual intercourse, tissue damage during childbirth, the presence of vulvar piercing, surgery, radiotherapy, and scars can be trauma inducers. The irritation process due to chronic exposure to urine should also be considered **[1]**.

Another factor to be taken into account is the hormonal influence, especially the defect in androgen action, due to low circulatory levels or reduction of receptors, as well as in cases of iatrogenesis due to suppression. At menarche, it is known that there is an increase in testosterone metabolism in the genital skin,

which has been referred to as one of the changes responsible for the increased incidence of VLS at this age [6]. In addition, overweight, obesity, and systemic arterial hypertension indicate that metabolic syndrome may be a possible target in predisposed individuals [21].

The interaction of the aforementioned items may result in immunological imbalance and inflammatory response, which are an important part of the pathophysiological mechanism. Evidence suggests that 21.5% to 34% of patients with VLS may have one or more associated autoimmune diseases such as thyroiditis, alopecia areata, vitiligo, and pernicious anemia [1,4,6,11]. Less frequent is the association with rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and scleroderma. Autoantibodies have been found in up to 74% of VLS carriers [6].

There is abnormal activation of the Th1-type inflammatory response cascade, which results in hypersecretion of pro-inflammatory cytokines such as IL-1, IL-7, IL-15, IFN-γ, TNF-α, and the IL-2 receptor (CD25). It is worth remembering that all of these mediators are associated with both the inflammatory process and collagen/fibroblast metabolism [1].

The CD4+ cell subpopulation, known as Treg, plays a crucial role in maintaining immunological tolerance. CD4+ Treg express high levels of IL-2 receptor α chain CD25high and CD127low, which are markers and transcripts of Forkhead box proteins (FoxP3), which are responsible for maintaining the suppressor phenotype and stability against infection, tumors, inflammation, allergy and autoimmunity [21].

Tissues with VLS present a deficiency in Treg activity, which can be measured by low FoxP3 expression; this phenomenon has also been observed in other autoimmune skin diseases such as pemphigus, psoriasis, and atopic dermatitis [22]. Systemic Treg dysfunction is expressed by the reduction of circulating CD127, which is a phenotypic marker of CD4+ and CD25+ [1]. Furthermore, chronic inflammation induces the production of reactive oxygen species (ROS), which contributes to tissue damage, resulting in sclerosis and scarring [1].

It is known that stimulation of fibroblast growth and activity, as well as abnormal collagen synthesis, leads to the progressive formation of hyalinized, sclerotic tissue in the dermis [1]. Secretion of fibroblast growth factors such as TGFβ and GDF15 has been observed. Furthermore, there are indications that overexpression of miR-155 decreases the levels of FOXO3 and CDKN1B and, therefore, promotes fibroblast proliferation. Thus, all these findings favor the stimulation of fibroblast growth [22].

Another point to be highlighted is the remodeling of collagen, especially due to the increased immune distribution of metalloproteinases such as MMP-2 and MMP-9 and TIMP-1 and TIMP-2 in the skin of patients with lichen sclerosus vulvae to normal vulvar skin. Additionally, an increase in type V collagen and gelatin-7 was observed, which influences collagen viability [1].

The formation of new epitopes was observed, which is extracellular matrix protein 1 (ECM1), important in the structural organization of the dermis, and controls not only keratinocytes but also angiogenesis, which may contribute to chronic ischemia [1]. Thus, loss-of-function mutations in the ECM1 gene are involved in the formation of IgG autoantibodies against ECM1, anti-BP180, and anti-BP230, acting as an epiphenomenon [1,5]. This entire pathophysiological process culminates in the dermo-epidermal alterations of VLS and is the definitive key to the histopathological findings of the disease [1].

There is no definitive cure for VLS, especially because its pathophysiology is not fully understood. It is important to emphasize that VLS should always be treated, even if asymptomatic, due to its progressive nature and its possible progression to cancer [1,11,22]. The most challenging aspect is recurrence after treatment is discontinued.

Two main targets for treatment can be identified as autoimmune mechanisms, followed by inflammation/oxidative stress and the formation of fibrotic tissue. The choice of appropriate treatment should be individualized and guided by common sense, depending on several factors, including severity and duration of disease, clinical findings, patient age, expectations, and improvement in quality of life. Effective management of VLS leads to improved quality of life, which emphasizes the importance of interventions designed with a focus on each patient [1,11,15].

The use of highly potent topical corticosteroids as therapy for the acute phase and prolonged maintenance is the standard treatment. The most commonly prescribed corticosteroid is clobetasol propionate 0.05%, in ointment or cream form [1,2,11,22]. The ointment is more potent than the cream [22]. The indication for the first line of treatment is based on the anti-inflammatory action of the corticosteroid, due to its interaction with intracellular glucocorticoid receptors and the induction of the production of proteins with anti-inflammatory action. These actions induce the reduction not only of structural damage but also of the risk of squamous cell carcinoma [1,2,22].

It has an excellent effect both in controlling the

disease and in reversing clinical and anatomopathological findings. Treatment of the acute phase should last at least 12 weeks, with daily use, once or twice, depending on the characteristics of the corticosteroid used. The regimen may be continuous use or gradual dose reduction, to avoid tachyphylaxis and promote the reduction of adverse effects. It is known that these two proposed regimens have equivalent efficacy and tolerability **[1,6]**.

Approximately 60 to 70% of patients experience complete remission of their symptoms, but those who persist with the sudden burning sensation or who experience late remission, only after 12 weeks, are indicative of the need for continued treatment, on a maintenance basis **[22]**. The most common adverse effects of high-potency corticosteroids are irritation, burning, dryness, hypopigmentation, atrophy, telangiectasia, or infection **[1,22]**.

In cases of resistance, one of the alternative treatments is the use of intralesional steroid injection. It should be noted, however, that failure to respond to treatment is multifactorial and should be investigated before considering changing the therapeutic strategy, especially laser therapy **[1,2]**. The unanimous aspect in the world literature is the indication of prolonged maintenance therapy, after treatment of the acute phase, to prevent or at least delay recurrences **[1,22]**.

In conditions of chronic treatment and monitoring, it is of fundamental importance that the attending physician discusses with each patient the need for prolonged maintenance of the treatment since 40% of patients have a phobia of the use of corticosteroids, which leads to some dystocias such as delaying the start of treatment as well as premature withdrawal of the medication **[2,22]**.

The severity of the disease is measured by the degree of hyperkeratosis of the lesion, and a favorable response to treatment is considered when the vulvar skin returns to its normal appearance, in terms of color and texture. This response is what guides the dose and duration of corticosteroid treatment, although monitoring and further research are necessary. Less potent topical corticosteroids, such as mometasone furoate 0.1% or triamcinolone, have also been shown to be effective, but are predominantly indicated in the maintenance phase, not as an attack phase drug **[22]**.

If the response is favorable, that is, if there is a reduction in signs and symptoms, maintenance therapy should be started. One option may be to reduce the dose or potency of the corticosteroid or to use ultra-potent corticosteroids intermittently, associated with tacrolimus ointment on weekends. Many other medications from different pharmacological classes are being tested and recommended in this phase of treatment. The use of emollients is an important complement **[22]**.

The recommended clinical follow-up consists of medical visits every three to six months, depending on the severity of the disease or complications, for two consecutive years, followed by annual visits for a prolonged period **[22]**. Intralesional application of triamcinolone acetonide is an alternative treatment to topical corticosteroids, but few studies support this indication. If the lack of response to topical treatment is due to difficulty in penetrating the drug deeper into the lesion, there may be benefits in using this route. In situations where itching is intense, it has been observed that there is a benefit in using combined therapy, that is, daily ultra-potent topical corticosteroid combined with intralesional corticosteroid, once a month, for two to three months. Combined therapy provides a prolonged and faster response compared to topical application, despite the discomfort of the injection **[6,22-24]**.

Calcineurin inhibitors, such as tacrolimus (0.1%) and pimecrolimus (1%) in topical preparation, are effective and safe and are considered an alternative option to the prolonged use of high-potency corticosteroids for maintenance. It is important to emphasize that the action of the latter is greater **[1,22,24]**. Calcineurin inhibitors reduce inflammation and pruritus by suppressing the release of cytokines by T cells and inhibiting the encoding of IL-3, IL4, IL-5, as well as granulocytemacrophage stimulating factor **[6]**.

They have immunosuppressive action and two daily applications are recommended for eight to 24 weeks. Complete remission was 43% and partial response was 34% after the use of tacrolimus. Combination therapy with corticosteroids has been considered. A burning sensation that disappears during treatment is mentioned as an adverse effect, without the need to discontinue the medication. Studies show that its use in the form of short treatment pulses does not increase the risk of squamous cell carcinoma **[1,6,22,24]**.

The use of topical retinoid may be the third choice for the treatment of VLS, both due to the lack of consistent scientific evidence of its effectiveness in VLS and due to its well-known side effect. This drug has the characteristic of normalizing the keratinization process and collagen metabolism, in addition to antiinflammatory action. VLS erythema with a burning sensation is cited as an adverse effect. This drug is contraindicated during pregnancy due to its probable teratogenic effect **[1,6,22,24]**.

Calcipotriol, which is the active form of vitamin D, acts to reduce keratocyte proliferation and inhibit the

inflammatory response mediated by T cells **[1,22,24]**. Oxatomide 5% gel is an antihistamine with anti-inflammatory action. Human fibroblast lysate cream contains anti-inflammatory cytokines such as IL-1RA, IL-10, IL-13 and growth factors EGF, FGFs and VEGF **[1]**.

Avocado and soybean oil extract with anti-inflammatory effect **[1,22,24]**. Heterologous type I collagen stimulates the proliferation of fibroblasts and extracellular matrix, but the results of this treatment modality are still preliminary **[1,24]**. In the early experimental phase, the administration of *Bifidobacterium infantis* is being used to promote an immune response by inducing the secretion of FoxP3 and IL-10. Thus, *Bifidobacterium infantis* could be included as an intervention to confer maximum immunomodulatory tolerance activity in the intestine to protect against inflammatory processes **[19]**.

In addition, cyclosporine and methotrexate are immunosuppressants and are considered an alternative for the treatment of refractory and severe forms. Immunobiologicals, such as adalimumab, are in the experimental phase **[22]**. Fat grafting is a second-line support measure in the treatment of VLS, indicated in cases of resistance or for anatomical repair to improve sexual function, as well as improve quality of life **[22,24]**. In adipose tissue, there are cells derived from stem cells that are capable of differentiating into different mesenchymal tissues, in addition to producing anti-inflammatory and immunomodulatory effects. It is a promising therapy but is in the experimental phase **[22]**.

Platelet-rich plasma therapy and adipose-derived stem cells. In relation, platelet-rich plasma therapy acts as a regenerative agent that stimulates cell growth and promotes migration, repair, and proliferation. While adipose is considered a stem cell transplant, therefore, due to its regenerative potential, it is appropriate to inhibit fibrosis, by acting in the remodeling of the extracellular matrix. The cells proliferate and differentiate into different mesenchymal tissues, in addition to presenting anti-inflammatory and immunomodulatory properties. These therapies are in an experimental stage and require further studies to provide better evidence **[1,22,24]**.

The use of acitretin, a synthetic retinoid, and potassium para-aminobenzoate are in the experimental phase **[1,24]**. Ultraviolet phototherapy UV-A1 is effective in sclerotic skin diseases. Its action is to inhibit collagen synthesis and induce the release of cytokines mediated by fibroblasts, in addition to being a powerful melatogenic, VLS in the re-pigmentation of the skin **[1]**. However, its results are inferior to the use of topical corticosteroids, therefore this therapeutic option is restricted to refractory cases **[1,22,24]**.

Photodynamic therapy, with the use of 5-aminoVLSulinic acid cream (5ALA at 10%), as a protocol before irradiation with red light at 100 mW/cm^2 **[22]**. Activation by protoporphyrins induces the production of ROS that causes apoptosis of lymphocytes and keratocytes **[22]**. The main side effect is pain with moderate to severe intensity and burning during the irradiation period. In case of recurrence, corticosteroids can be used again as palliative therapy, and if control is still not achieved, new phototherapy sessions can be performed until the recurrence and remaining lesions are stabilized **[1,22,24]**.

Besides, ablative and non-ablative laser is considered an adequate treatment alternative for VLS, although it is a costly procedure. Laser induces neovascularization, formation of collagen and elastic fibers, and reduces epithelial degeneration and atrophy. A randomized study with Nd: YAG laser for 14 days, associated with beclomethasone versus a control group that was treated with topical corticosteroids for four weeks in a decreasing dose, showed that the Nd: YAG laser group presented improvement in symptoms and better satisfaction than the control group **[25]**. However, there is no evidence, with long-term longitudinal studies, after the use of the laser, therefore, maintenance therapy with high-potency corticosteroids is still the standard therapy **[1,14,22,25]**. Ablative laser such as carbon dioxide is indicated for cases of severe VLS, but the evidence is weak, as the studies are heterogeneous and there is no comparative study, therefore, there is no consensus **[1,22]**. The results of an Italian clinical study, called MonaLisa Touch Laser (Trail number NCTO3665584), are being eagerly awaited; it is an RCT comparing the use of $FxCO_2$ laser and Shan laser, in 40 patients **[22]**.

Mutilating surgeries are not recommended in VLS. Surgery is indicated for diseases that are refractory to clinical treatment, symptoms of urinary obstruction, association with neoplasia, or for aesthetic reasons **[1,6,22]**.

Emollients are considered an integral part of VLS treatment, their function being to soften and protect the skin from fissures, as well as replace soaps. The use of moisturizers and paraffin form a protective barrier to urine, which reduces VLS symptoms. Emollients and lubricants should be used during sexual intercourse to avoid pain. There is no contraindication to the chronic and prolonged use of these products, as they are safe and low-cost **[1,22,24]**.

Agents such as chamomile, coconut oil, shea butter (an African tree whose seeds are oily), aloe vera, calendula, arnica, avocado, etc. have shown variable and controversial results, with their application in cases

of moderate to severe VLS, especially among women who prefer to avoid prolonged use of corticosteroids **[6,22,24]**.

It is argued that products rich in oxalate can worsen symptoms, as has been the result of studies on vegetables such as spinach; legumes such as potatoes, beets, turnips; seeds, coconuts, and canned or boxed products. Symptoms have been reported to worsen with the consumption of pork **[22]**. As for dietary supplementation with vitamin E, there is no consistent evidence in favor **[6]**.

Diets rich in trans fatty acids increase the number of harmful microorganisms such as Desulfovibrionaceae and Protebacteria while suppressing beneficial ones such as Bacteroides. This diet associated with alcohol consumption can delay healing by exacerbating the inflammatory process and oxidative stress **[15]**. Diets rich in vegetable protein increase the proportion of short-chain fatty acids (SCFA), which are important for maintaining the integrity of the mucosa, and a diet rich in collagen protects the skin from aging. The metabolic process of a diet rich in fiber induces the growth of bacteria, including lactobacilli. A diet rich in complex carbohydrates can be converted into SCFA, inducing several anti-inflammatory effects: improving the integrity of the intestinal barrier, modulating respiratory diseases, preventing inflammatory diseases, and regulating lipid and glucose metabolism; in addition, SCFA plays a role in the expression of FoxP3, which helps in the development and function of Tregs, improving the regulatory function of T cells **[26]**.

The use of probiotics containing *Lactobacillus reuter* RC-14 and *Lactobacillus rhamnosus* GR-1 can help the vaginal microbiome and reduce pruritus, improving genital discomfort; in addition to improving the body's defense against opportunistic infections such as candida and herpes, especially in chronic use of corticosteroids **[22]**. As previously mentioned, patients should be advised not to use soaps, but rather emollients, moisturizers, and lubricants. It is important to advise that underwear fabrics should be soft, delicate, light, and airy, and should not cause friction. It is preferable to use silk underwear rather than cotton **[22,26]**.

The increased risk of vulvar cancer should always be emphasized, so these women should be encouraged to self-examine their vulva and should observe any changes in the skin, color, texture, or appearance of ulcerative lesions. When selfexamination is difficult, for example in the case of obese, elderly, or visually impaired patients, the physician should be alert and schedule follow-up visits for clinical visits in a shorter period **[1,22,26]**. Two other points, no less important, are advice on the treatment of asymptomatic patients to prevent bedsores and psychological counseling in the care routine **[1,22]**.

Patients must be advised to access reliable websites via the Internet for additional information, and the Kathy Ruiz-Carter Lichen Sclerosus Support Network website, which has a Portuguese version, fulfills this role well. It provides guidance on the disease, treatment, and the implications of diet for symptoms, in addition to promoting virtual discussion meetings to clarify doubts and exchange experiences **[27]**.

The guidance on the frequency of medical visits was detailed in previous topics in this manuscript. It is important to emphasize that at each follow-up visit, the specialist must observe adherence to treatment, objective and symptomatic response, need for maintenance therapy, appearance of adhesions, bedsores, or even adverse effects of treatment. In addition, the specialist must always be available for additional medical guidance and clarification of doubts **[1,22,24,26]**.

Conclusion

It was concluded that the exact cause of vulvar lichen sclerosus is not fully understood, but it is believed that nutritional factors, dysbiosis of the intestinal microbiota, genetics, autoimmunity, and hormonal imbalance may play an important role in its development. The main risk factor for vulvar cancer associated with vulvar lichen sclerosus is delayed diagnosis, so controlling symptoms and preventing complications is crucial, and regular follow-up is necessary to monitor the response to treatment and recurrence of the disease.

CRediT

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