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Review Article

Advances in Understanding Vulva Lichen Sclerosus: Pathogenesis and Treatment

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Abstract

Vulva lichen sclerosus (VLS) is a chronic, painful, inflammatory disease that has a significant impact on quality of life. The treatment goal is to relieve symptoms, reverse the condition, and prevent anatomical changes. Currently, there have been numerous reported treatment approaches for this disease, but the outcomes are not satisfactory, and there is no definitive cure. This may be due to the fact that the exact pathogenesis of VLS remains unknown. Possible mechanisms of VLS development include immune factors, genetic factors, hormonal factors, local environmental factors, and infectious factors. Current treatment options for VLS include Western medicine, traditional Chinese medicine, integrated Chinese-Western medicine, focused ultrasound, and dot matrix therapy, etc. The preferred medication for controlling itching symptoms is glucocorticoid drugs, which have a certain effect on the treatment of this disease. This article summarizes the latest advances in the pathogenesis and treatment methods of VLS, aiming to provide reference and assistance for clinical physicians in understanding and treating this condition.

Introduction

Vulva lichen sclerosus (VLS) is a chronic, inflammatory, progressive dermatological condition primarily affecting the anogenital region [1]. While this disease can occur in individuals of all ages and both sexes, it is more common in females than males. The exact prevalence of VLS is unclear, but it is estimated to be 0.1% before puberty and 3% after menopause [2]. Recent research suggests that immune factors, inflammatory infections, cellular apoptosis and proliferation, genetics, and local irritants may contribute to the development of this condition.

Currently, there is no specific curative treatment for VLS. Management mainly focuses on relieving clinical symptoms, halting disease progression, and utilizing a combination of Traditional Chinese Medicine, Western medicine, or integrative approaches. Local medication and physical methods are the primary modalities employed in treatment [3]. This article provides a comprehensive review of recent research on vulvar white lesions, aiming to assist clinical practitioners in understanding, diagnosing, and treating this condition.

Progress in Pathogenesis Mechanisms

To date, the etiology and pathogenesis of VLS remain unclear. Existing evidence suggests that immune dysregulation and chronic inflammation, operating against a genetic background, play a role in the development of this condition triggered by certain factors. Additionally, the promotion of fibroblast growth and activity, as well as collagen synthesis, leading to the progressive formation of transparent and sclerotic dermal tissue, represents another key factor in the pathogenesis of VLS [4].

Immune Factors

In females, VLS is considered to be an autoimmune disease. It exhibits characteristics consistent with other autoimmune diseases, including a higher prevalence in females and positive correlations with other female autoimmune conditions [5]. The

most common autoimmune diseases associated with female VLS include thyroid disorders, alopecia areata, vitiligo, pernicious anemia, psoriasis, diabetes, asthma, and rheumatoid arthritis [6,7].

Gene expression profiling supports VLS as an inflammatory disease mediated by upregulation of T helper type 1 (Th1) cytokines. A well-established link exists between Th1 responses and autoimmune diseases [7,8]. Furthermore, research indicates that the pathogenesis of vulva lichen sclerosus may be related to Th1 cytokines such as IFN-γ and epithelial-derived IgG, rather than Th2 or Th17 cytokines and HD-5 [9].

Studies also suggest that reduced activity of regulatory T cells (Tregs) may be present in VLS tissues. Tregs play a crucial role in maintaining immune tolerance. Consequently, decreased Treg function may lead to impaired self-antigen immune tolerance and autoimmune dysfunction. Compared to the control group, overexpression of microRNA-155 in VLS patient tissues is believed to inhibit Treg cell activity [10]. Foxp3, a marker and key regulatory factor of Treg cells, may further contribute to the compromised immune suppressive function of this lymphocyte subset in VLS due to its low expression in affected areas [11].

Genetic Factors

While the exact etiology of VLS remains unclear, there is evidence to suggest that the disease is an autoimmune disorder with genetic associations. Sherman et al. [12] conducted a study involving 1,052 patients, of whom 126 (12%) had a positive family history of lichen sclerosus (LS). These patients were from 95 families, and those with a family history of VLS had a significantly higher incidence of vulvar cancer compared to those without a family history (4.1% vs. 1.2%, $P<0.05$). The correlation between familial VLS and autoimmune diseases was greater than that of sporadic VLS.

Human leukocyte antigen class II (HLA-II) antigens play a crucial role in humoral immunity regulation. Studies have shown that genetic susceptibility to VLS can be significantly enhanced through positive modulation of HLA-II antigen genes [7]. Compared to the control group, VLS females have increased prevalence rates of HLA-DQ7, -DQ8, -DQ9, and -DR12. Among them, 50% of adult females and 66% of prepubertal females express HLA-DQ7 [13].

A study comparing the genomes of VLS patients with unaffected relatives using whole-exome sequencing revealed the presence of recurrent germline variants in genes encoding proteins involved in immune regulation and/or tumor suppression activity. Examples of these genes include CD177, CD200, ANKRD18A, and LATS2, which may be key factors in the pathogenesis of VLS [14].

Hormonal Factors

In recent years, increasing evidence has indicated that disturbances in endogenous hormone levels play an important role in vulvar white lesions. Additionally, the higher incidence of vulvar lichen sclerosus (VLS) in postmenopausal women and prepubertal girls with low estrogen levels suggests a possible association with hormonal influence [7]. Studies by Zhu Lihong et al. [15] demonstrated that patients with vulvar lichen sclerosus have decreased levels of serum estradiol and dihydrotestosterone, which are negatively correlated with the extent of vulvar white lesions. Furthermore, the analysis revealed significantly lower serum hormone levels in recurrent VLS patients compared to those with initial onset, indicating a negative correlation between serum hormone levels and disease severity in vulvar lichen sclerosus. Low levels of dihydrotestosterone and estradiol are associated with disease recurrence.

Local Environmental Factors

The unique anatomical location of the vulva makes it susceptible to irritants such as urine, menstrual fluid, and vaginal secretions. Studies have suggested that the occurrence of vulvar white lesions may be associated with a moist vulvar environment and exposure to urine, menstrual fluid, feces, as well as irritation from hygiene products [16]. In males, lichen sclerosus is more common in individuals with urinary tract obstruction, those who have not undergone circumcision, and those who have undergone urethral surgery. Additionally, it is known that lichen sclerosus tends to occur at sites of trauma, known as the Koebner phenomenon [17]. Lichen sclerosus can occur at surgical wounds, sunburned areas, post-radiation sites, and in patients with scarring after perineal episiotomy. Extragenital lichen sclerosus can develop in frictional areas such as the axilla and inframammary region [18].

Infectious Factors

In some patients with vulvar white lesions, vaginal infections can be present, including Candida species, Treponema pallidum, and Escherichia coli. Klaus Eisendle et al. [19] used focused floating microscopy to observe tissue sections from VLS patients, and their findings indicated that, especially in early lichen sclerosus, Treponema pallidum or similar strains were frequently detected, suggesting their involvement in the development of the disease or as one of the triggering factors. Hald AK et al. [19] reviewed 27 studies investigating the relationship between VLS and HPV and found that among all VLS cases, the HPV positivity rate ranged from 0% to 80%, with a median of 22%. The prevalence of HPV infection was higher in male VLS patients (median 29%) compared to female patients (median 8%). HPV type 16 was the most common genotype, but the distribution of genotypes suggested that even low-risk HPV could potentially

contribute to VLS. A dysbiosis in the skin and gut microbiota has been observed in the microbiomes of VLS patients, including Prevotella species, Streptococcus species, and Porphyromonas species. In comparison to healthy individuals, an enrichment of Finegoldia species was found in several skin areas of VLS girls. In fecal samples, there was a significant increase in the relative abundance of Dialister, Clostridium difficile, Escherichia coli, Bifidobacterium, and Bacteroides in VLS patients compared to the control group [20]. Alterations in the skin and gut microbiota, as seen in other inflammatory skin conditions, may contribute to the inflammatory progression in VLS through the modulation of systemic immunity [21].

Treatment Progress

This condition is characterized by easy diagnosis but difficult treatment. Early diagnosis and intervention can improve long-term prognosis for patients. However, the current understanding of vulva lichen sclerosus (VLS) in the domestic academic community (including gynecology and dermatology) is not yet unified. Only 90% of patients with itching symptoms seek medical attention, while approximately 10% of asymptomatic patients are either missed or misdiagnosed. There are significant regional differences in treatment approaches. The objectives of treatment are to alleviate itching and pain symptoms, prevent anatomical changes caused by scarring, and prevent possible malignant transformation [22].

Western Medicine Treatment

Topical corticosteroids are a more effective treatment method and can effectively relieve itching and control disease progression. Lee et al. [23] treated and regularly followed up with 507 female VLS patients using a conventional, long-term, individualized preventive topical corticosteroid (TCS) treatment regimen. The treatment plan matched the efficacy and duration of TCS treatment with the objective severity of the disease. Once patients achieved clinical remission, TCS was used preventively and regularly. The long-term goal was to preserve normal skin color and texture, rather than just controlling symptoms. This approach has yielded good treatment results and has been shown, in this cohort study, to not only improve function and alleviate symptoms but also reduce the development or progression of scarring and eliminate the risk of cancer. No significant adverse reactions were encountered, and cases of reversible skin atrophy were rare. These data recommend this treatment strategy based on objective disease suppression and symptom control, with regular follow-up to optimize compliance, adjust treatment efficacy, and monitor complications. The Consensus on the Clinical Diagnosis and Treatment of Vulvar Lichen Sclerosus in Women (2021 Edition) [24] indicates that topical corticosteroids are the first-line treatment for VLS, divided into an induction and maintenance phase. The induction phase recommends the use of topical corticosteroid ointment or cream for a continuous period of 3-4 months. Clinical symptoms disappear in over 50% of patients, and skin lesions such as excessive keratinization, bleeding, and fissures show significant improvement. In the maintenance phase, low-dose topical corticosteroid ointment or cream is used lifelong to control vulvar symptoms, reduce recurrence rates, and lower the risk of vulvar adhesion formation and malignancy. 0.05% clobetasol propionate ointment is recommended as the preferred topical corticosteroid for VLS treatment. Yang Min et al. [25] demonstrated the good efficacy and safety with minimal adverse reactions when using 0.05% halometasone cream to treat vulvar lichen sclerosus.

Integrated Chinese and Western Medicine Treatment

Wang Wei et al. [26] divided 50 patients with vulvar leukoplakia into a control group and an experimental group. The control group received treatment with topical application of Western medicine ointment combined with local phototherapy using a Bomo lamp. The treatment group received additional herbal fumigation with a skin-soothing wash and topical application of a Chinese herbal formulation based on the treatment methods used in the control group. The total effective rate was 80.0% (20/25) in the control group and 100.0% (25/25) in the treatment group. The difference between the two groups was statistically significant ($P<0.05$), indicating that the clinical efficacy of the treatment group was superior to that of the control group. The integrated Chinese and Western medicine comprehensive therapy showed significant effectiveness in treating vulvar leukoplakia and is worthy of clinical promotion and application [26]. Shen Fengming et al. [27] used a self-developed anti-itch external wash combined with self-prepared Western medicine ointment for topical application in the treatment of vulvar leukoplakia. The total effective rate in their study was higher than the treatment effects reported in the literature using Western medicine corticosteroids, androgens, and local immune suppressants [28]. Jiang Junqing et al. [29] observed the clinical efficacy of topical tacrolimus ointment combined with oral Chinese herbal medicine in the treatment of vulvar lichen sclerosus. The results indicated that the combination of topical tacrolimus ointment and oral Chinese herbal medicine had a good therapeutic effect on vulvar lichen sclerosus and showed significantly better efficacy than the use of topical tacrolimus ointment alone.

Focused Ultrasound and Fractional CO_2 Laser Treatment

Hou Yanan et al. [30] conducted a study comparing the treatment effects of fractional CO2 laser therapy in 49 cases and focused ultrasound therapy in 50 cases for vulvar leukoplakia. The results indicated that both fractional CO2 laser and focused ultrasound were effective methods for treating vulvar leukoplakia. In terms of short-term improvement in dyspareunia and increased

sexual satisfaction, laser therapy showed more pronounced effects. In terms of skin color improvement, focused ultrasound may be more effective. Focused ultrasound was applied to disrupt the lesions in the dermis and subcutaneous tissues, improve microcirculation and nerve terminal nutrition, and promote tissue reconstruction and repair. The results of a study by Mi Meiyan [31] demonstrated that focused ultrasound treatment had a higher cure rate and lower recurrence rate compared to microwave therapy for vulvar leukoplakia, without damage to the surrounding tissues. It is a safe, effective, non-invasive, and reliable new method. Zhao Yan et al. [32] compared the treatment effects between focused ultrasound therapy and fractional CO2 laser therapy, and the results showed that the total effective rate in the fractional CO2 laser group [94.44% (34/36)] was higher than that in the focused ultrasound group [74.29% (26/35)] ($p<0.05$). Fractional CO2 laser treatment had significant effects in reducing female distress, improving quality of life, and had fewer adverse reactions and a lower recurrence rate in patients with vulvar leukoplakia.

Surgery and Other Treatments

Surgery does not cure the disease but is only applicable to patients who have failed both drug and physical therapy, have severe destruction of the vulvar morphology that affects their quality of life, or have developed malignancy. After surgery, maintenance therapy with medication should be promptly initiated to control disease progression. Photodynamic therapy has shown good efficacy in improving pruritus symptoms and enhancing quality of life, with minimal damage, making it one of the treatment options [33]. Local cryotherapy with liquid nitrogen, microwave therapy, medical computer high-frequency electrosection, helium-neon laser local irradiation, and infrared local thermotherapy with Bo-Nuan are also effective to some extent.

Summary

The pathogenesis of vulvar lichen sclerosus (VLS) is associated with multiple factors, including immune factors, genetic factors, and infectious factors. Currently, there is a lack of treatment options that provide stable efficacy and prevent recurrence [22]. The ultimate goal for VLS patients undergoing specific treatments is to no longer be affected by symptoms such as pain and sexual dysfunction in their daily lives. Achieving objective normalcy in skin color and texture is a further crucial milestone in treatment. Additionally, the purpose of treatment is also to prevent the development of more severe forms of the disease, such as vulvar malignancies [4]. In recent years, topical glucocorticoids have been preferred as the first-line treatment, showing good effectiveness in controlling disease progression. For a minority of patients who do not respond well to treatment, other appropriate treatment methods can be chosen based on individual circumstances. In the future, more research is needed to elucidate the pathogenesis of this disease and provide new drugs and approaches for its improved management.

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