Review Article

Research advances and new treatment strategies for non-neoplastic epithelial disorders of the vulva: a narrative review

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Background and Objective: Vulvar dermatoses are common, potentially debilitating conditions that can be seen by a variety of medical specialists. Lichenoid vulvar diseases, namely lichen sclerosus (LS) and lichen simplex chronicus (LSC) can all negatively impact patients' quality of life and LS and LP also have an association with squamous cell carcinoma. Herein, we provide an update on the epidemiology, clinical presentation, histopathology, and treatment of patients with vulvar LS and LSC.

Methods: We searched The Cochrane Central Register of Controlled Trials (CENTRAL), The National Research Register, Health technology assessment database(HTA), MEDLINE, EMbase, CancerLit, CBMdisc, VIP, PubMed and CNKI medical databases for English and Chinese literature of lichen sclerosus (LS) and lichen simplex chronicus (LSC) published since January 1st,1987.

Key Content and Findings: The exact etiology pathogenesis of Non-neoplastic epithelial disorders of the vulva (NNEDV) remains unclear. It may be associated with autoimmunity, local factors, heredity, infection, and hormone levels. Pathological biopsy is the cornerstone for establishing a definitive diagnosis. The currently available treatments have their own advantages and disadvantages. Corticosteroid therapy is a classic clinical treatment, and more recent therapies including matrix CO2 laser resurfacing, PDT, stimulation of vascular smooth muscle, and ADSC injection have also shown good efficacy.

Conclusions: More effective and safe approaches for NNEDV prevention and treatment are expected to occur with the advance of research in the etiology and pathogenesis of this disease.

Keywords: Treatment; advances; research; chronic lichen simplex chronicus; lichen sclerosus

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Introduction

Non-neoplastic epithelial disorders of the vulva (NNEDVs), also known as vulvar dystrophy or white lesions (or leukoplakia) of the vulva, are a group of chronic diseases occurring in females, manifesting as degeneration of the vulval skin along with mucosa and pigment changes. Based on their pathologic types, NNEDVs can be divided into lichen sclerosus (LS) and lichen simplex chronicus (LSC). The typical clinical manifestations of NNEDV include: intensive vulvar itching and pain; rough vulvar skin, showing lichenification, local hypopigmentation, and even rhagades and atrophy; and in severe cases, the development of atrophy of both the greater and lesser lips of the pudendum along with adhesions, both of which seriously affect the sexual and urinary function as well as quality of life.

The pathogenesis of NNEDV remains unclear. Despite

a plethora of clinical investigation on the pathogenesis and treatment of this disease, no widely recognized treatment is available. Although symptomatic treatments with topical hydrocortisone or traditional Chinese herbal medicine have shown certain efficacy, the disease is still incurable, and the recurrence rate after treatment remains high. This article summarizes the recent research advances and new treatment strategies for NNEDV.

Methods

We searched The Cochrane Central Register of Controlled Trials(CENTRAL), The National Research Register, Health technology assessment database(HTA), MEDLINE, EMbase, CancerLit, CBMdisc, VIP, PubMed and CNKI medical databases for English and Chinese literature of lichen sclerosus (LS) and lichen simplex chronicus (LSC) published since January 1st,1987. The criteria for inclusion are that During the period from November 2016 to July 2018, there were 98 patients with vulvar simple lichen/ sclerosing lichen confirmed by vulvar biopsy in the second Hospital of West China of Sichuan University. All patients voluntarily participated in this trial and signed the informed consent form of clinical study, Exclusion criteria: (I) pregnancy or recent fertility requirements; (II) photosensitive history; (III) severe systemic medical diseases that have affected daily life (such as diagnosis of severe cardiovascular and immune system diseases); (IV) patients with psychological and mental diseases such as depression, unable to complete follow-up; (V) patients who received other physiotherapy in the past 3 months; (VI) atypical hyperplasia or vulvar cancer of the vulva; (VII) patients with diabetes. (VIII) patients with other special skin diseases, (IX) patients with reproductive system tumors and acute inflammation. Outcomes of interest include terminology and classification, epidemiology, etiology and pathogenesis, clinical features, diagnosis and treatment. Study selection will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Two reviewers will independently select the studies and assess their eligibility. Two other reviewers will independently extract data from each study.

Terminology and classification

NNEDVs are a group of chronic diseases in which the vulvar skin and mucosal tissues undergo degeneration and pigmentation. For many years, the nomenclature of the disease was not unified. Since the vulvar skin and mucosa of patients with LS or squamous epithelial cell hyperplasia are often white, NNEDV is also called white lesions of the vulva. The names of LS and squamous epithelial cell hyperplasia have changed frequently (e.g., vulvar leukoplakia, leukoplakic vulvitis, kraurosis vulvae, proliferative or atrophic female vulva inflammation, and lichen sclerosus et atrophicus) in the past decades due to different clinical and pathological understandings. To eliminate such confusions, the International Society for the Study of Vulvovaginal Disease (ISSVD) replaced the 1987 classification with a new, histopathological classification method to enable clinicians to diagnose NNEDVs more accurately. In 2011, the ISSVD released a classification system based solely on clinical manifestations. These two classifications complement each other and optimize the clinical diagnosis and treatment of NNEDVs (1). Lichen simplex chronicus (LSC) (spinous cell hyperplasia in the ISSVD 2006 classification) replaced squamous cell hyperplasia or proliferative dystrophy in the 1987 classification, while vulvar LS is one of the lichens or sclerotic subtypes in the ISSVD 2006 classification.

Epidemiology

NNEDV is a multidisciplinary disease, and patients seek treatment in different hospitals and departments, which makes an epidemiological survey of this disease more difficult. Large-sample surveys on NNEDVs have been carried out in several countries, yielding incidence rates of 1/300–1/1,000 (2).

No epidemiological data on NNEDVs from large-scale studies have been conducted in China. We carried out a cross-sectional survey based on the basic information of NNEDV patients who sought treatment in the Department of Gynecology West China Second University Hospital of Sichuan University from 2010 to 2015 as well as their pathological biopsy results, with an attempt to learn the prevalence and age distribution of NNEDV. It was found that NNEDV was a relatively common condition: 33,859 of 2,456,822 women visiting our outpatient offices in the Department of Gynecology were diagnosed with NNEDV, and the prevalence rate was 1.38% (3). The age distribution of two major NNEDV types differed: the prevalence of LSC was significantly higher than that of LS in the 20–40 age group, whereas the prevalence of LS was significantly higher than that of LSC in the 50–70 age group. Therefore, these two types may have different pathogenic mechanisms and molecular biology levels, and thus warrant further

investigation.

Clinical features

The main clinical manifestations of NNEDV include genital itching and tingling sensation, which are more obvious at night and can disturb sleep in severe cases. The persisting severe itching can lead to local subcutaneous bleeding of the vulva, which is often accompanied by vulvar squamous epithelial hyperplasia and ulceration. Long-term inflammatory stimulation causes vulvar anatomical changes and scar formation, leading to difficult or painful sexual intercourse.

Etiology and pathogenesis

The etiology and pathogenesis of NNEDV remain unclear and may be associated with the following factors.

Immunologic factors

Many studies have demonstrated that NNEDV may be associated with autoimmunity. Patients with LS often have other autoimmune diseases such as vitiligo, autoimmune thyroiditis, pernicious anemia, and alopecia areata. Cooper *et al.* (4) enrolled 190 patients with LS and found that 28% of these patients had one or more autoimmune-related diseases, and circulating autoantibodies were more likely to be detected in patients with LSC; in contrast, only 9% of healthy individuals (n=230) had autoimmune-related diseases. Terlou *et al.* (5) investigated the molecular and immunological mechanisms critical to the pathogenesis of LS and lichen planus. By using gene expression profiling and real-time RT-PCR experiments, the authors demonstrated a significantly increased expression of the pro-inflammatory cytokines (IFNγ, CXCR3, CXCL9, CXCL10, CXCL11, CCR5, CCL4, and CCL5) specific for a Th1 IFNγ-induced immune response. In addition, BIC/microRNA-155 (miR-155)—a microRNA involved in regulation of the immune response—was significantly upregulated in LS and lichen planus (9.5- and 17.7-fold change, respectively).

Genetic factors

Many clinical studies have reported the familial aggregation of NNEDV, suggesting the occurrence of this disease is related to genetic factors. Higgins *et al.* (6) showed that about 10% of women with chronic vulvar LS had relatives with the same disease. Sherman *et al.* (7) conducted a family history survey in 1052 patients diagnosed with vulvar LS and found 12% of them had a definite family history of LS. Gao *et al.* (8) compared the relevant genes between 187 females with LS and 354 normal women and found that patients with LS had significantly higher expressions of DRB1*12 (DR12) and haplotypes DRB1*12/DQB1*0301/04/09/010 than normal women; these genes may make the vulvar tissue become more susceptible to LS.

Infections

A Chinese study has indicated (9) that the vaginal flora are dysregulated in most patients with vulvar malnutrition, and that vaginitis caused by vaginal microecological imbalance may be related to the pathogenesis of NNEDV. It has also been reported that vulvar LS is associated with HPV infection, which may explain the development of vulval intraepithelial neoplasia (VIN) in LS cases. Studies have also found that vulvar LS is associated with *Chlamydia trachomatis* infection or other related infection histories.

Hormones

NNEDV can occur at any age, even in children. However, in most cases the disease occurs around menopause; in particular, LS is typically seen in women aged 50–60 years. As shown in our epidemiological survey (3), the youngest NNEDV patient was only 1 year old, and the age of onset increased from 20 years old to the highest peak in 40–50 years, and then descended successively; the prevalence of vulvar LS was higher than that of LSC in the population aged 50–70 years. Therefore, NNEDV may be related to the body's hormone levels. Gnther *et al.* believed that NNEDV was caused by an endocrine factor: sexual hormone deficiency. NNEDV typically occurs in perimenopausal women, and the serum levels of sexual hormones in NNEDV patients are lower than those in normal women of the same age, suggesting sexual hormones may contribute to the pathogenesis of LS (10). It has also been reported that the expressions of ER and PR receptors decreased in NNEDV patients, suggesting the occurrence of NNEDV may be related to estrogen and progesterone levels.

Local factors

In many NNEDV patients, the itching symptom follows

one other factor, often a fungal infection or other type of vaginitis. Condoms, rinses, lubricants, spermicides, soaps, disposable pads, and tampons are the common triggers for irritant contact dermatitis. It has been reported that local trauma of the vulva, repeated friction, surgery, or sexual abuse during childhood may be related to the occurrence of NNEDV. In addition, our epidemiological studies have shown that the incidence of NNEDV was significantly higher in Chengdu and southern Sichuan than in western and northern Sichuan areas, suggesting that the disease may be related to different living conditions such as environmental humidity and local diets, although its underlying mechanism needs further investigations.

Psychological factors and stress

Psychological factors may also play a crucial role in the development of NNEDV. Although most NNEDV patients do not actively express their feelings of depression or anxiety, quite a few of them are certain that their itching and subsequent scratching are exacerbated by stress. The relationships between mental/psychological factors and skin disorders are complex. Studies have suggested that the incidences of psoriasis, urticaria, and alopecia areata are associated with sensitive skin caused by psychological stress. Skin is one of the target areas of psychological stress, which ultimately affects the change of skin functional status and increases the risk of skin diseases. One possible explanation is that both skin tissue and the nervous system are derived from the ectoderm.

Diagnosis

Some authors argue that biopsy should be performed before treatment to achieve definite histopathological diagnosis of NNEDV (11). The diagnosis of LSC is often based on medical histories and physical examination. LSC usually affects the germinal layer of the labia majora, and physical examination can reveal epidermal thickening, lichenification of papules and plaques, and skin spots; also, skin biopsy can help diagnose unidentified conditions. The clinical diagnosis of early vulvar LS (LS) may be problematic; however, biopsy can help diagnose or rule out other conditions. For vulvar lesions with leathery appearance, the lesion margins should also be sampled during biopsy. The general clinical diagnosis will be adequate for pediatric patients with LS because biopsy is invasive and would better be applied for refractory cases only.

Treatment

Both LS and VLSC are chronic recurrent diseases, and LS can also lead to loss of vulvar structures and vulvar squamous cell carcinoma (VSCC). A recent study of 3,038 women diagnosed with LS found the cumulative VSCC incidence was 6.7% during the 20-year follow-up. For LS, VIN and age ≥70 years at the time of LS diagnosis were important risk factors for VSCC development (12). Therefore, treatment and long-term management of LS and VLSC are essential.

General treatment

Patient education is an important component of LS and VLSC management. Importantly, patients should be informed about the possible predisposing factors such as urinary incontinence and sweating. They should avoid using airtight clothes and underwear and quit bad habits such as long-term consumption of spicy food, smoking, and/or drinking. They should also be discouraged to excessively use detergents or irritating topical medications, which may cause itching and pain. Efforts should be made to improve sleep, increase exercise, and maintain a good mood. The management of VLSC also involves the treatment of any potential vulvar diseases, repair of barrier function, alleviation of inflammation, and elimination of the itch-scratch cycle. Treatment of any potential vulvar disease is equally important as it can enhance the therapeutic efficacy (even if not for NNEDV). Emollients can be used to repair the barrier function. In addition, emollients can improve symptoms and relieve itching. Gentle, non-scented emollients and soap-free detergents are recommended.

Medical treatment

Topical corticosteroids (TCS)

Backed by strong evidence, ultra-potent topical steroids have become the mainstream treatment for LS and VLSC. Ointment is the preferred drug because it is less irritating than other treatments. Ultra-potent topical steroids can also be used as first-line treatments for children, as their safety and effectiveness in prepubertal pediatric populations have been well demonstrated. Corticosteroids are particularly effective for thick hyperkeratotic plaques. A prospective study in 507 NNEDV women confirmed that long-term use of topical steroids reduced scarring

and dramatically lowered the risk of cancer while maintaining normal skin (13). A recent study has shown that topical use of corticosteroids during pregnancy was safe, and normal vaginal delivery was feasible after the topical use of corticosteroids (14). However, long-term use of steroids is required, as relapse can easily occur after drug withdrawal.

Topical calcineurin inhibitors

The role of topical calcineurin inhibitors (TCIs) in treating patients with LS and VLSC has been confirmed. It can be used to treat patients with topical corticosteroid insensitivity or intolerance and has now become a second-line treatment for LS and LSC. In 2006, a phase II trial on the safety and efficacy of 0.1% tacrolimus ointment in treating LS revealed that clearance of active LS was reached by 43% of patients at 24 weeks of treatment. Partial resolution was reached in 34% of patients. Although no adverse event occurred during the 18-month follow-up, theoretically, the topical immunosuppression could increase the risk of malignant transformation (15). Vulvar squamous cell carcinoma after treatment with topical immunosuppressive agents has been reported in adult patients, and there is not sufficient evidence to recommend the use of topical immunosuppressive agents for the treatment of LS. In fact, the topical immunosuppressive agents are more expensive and can easily cause stinging and burning sensations, and their long-term safety has not been established.

Other medications

Topical tretinoin has been applied as a monotherapy for VLS; however, there is still insufficient evidence concerning its therapeutic effect, and its irritancy also limits its clinical application (16). Because tretinoin is highly embryotoxic and teratogenic in human pregnancy, strict contraception should be started one month before medication. If isotretinoin or alitretinoin is used, the contraception should continue until one month after the end of treatment. If a retinoid is used, the contraception should continue until six months after the end of treatment, so as to ensure the complete metabolism of the drug in the body.

Similarly, topical estrogen has no value other than reducing vaginal atrophy caused by decreased estrogen levels in postmenopausal women. It is actually an important treatment for VLS in postmenopausal women but not a special treatment. However, since vaginal dryness and persistent pain are parts of the genitourinary syndrome of menopause (GSM), the use of topical estrogen can only relieve GSM rather than treating LS.

Treatments based on traditional Chinese medicine (TCM)

According to the theories of TCM, NNEDV is caused by dampness-heat of the liver channel, yin deficiency of the liver and kidney, yang deficiency of the spleen and kidney, blood deficiency transforming into dryness, and qi stagnation and blood stasis. It can clinically manifest as itching, skin hypopigmentation, and pain accompanied by skin atrophy and thickening. The TCM therapies for NNEDV include oral administration of TCM drugs, scrubbing the lesion with topical drugs, acupoint blocking, and acupuncture and moxibustion. These treatments have shown certain efficacy in clinical practice. However, the poor understanding of the etiologies and the diverse treatment methods have made it difficult to comprehensively evaluate the roles of TCM therapies.

Physical therapies

Matrix CO_2 laser resurfacing

The matrix CO_2 laser emits multiple tiny beams (sized 75–100 μm) with equally distributed energy through a focal lens. The beams are separated by normal tissues, which effectively reduces the damage of heat conduction. The mechanism of action of CO_2 laser is that the water molecules in the epidermis absorb the light energy, causing heat accumulation and subsequent ablation of the epidermis and superficial dermis. The dermis of patients with LS, especially the dermis near the dermis-epidermal junction, is theoretically characterized by dysregulated signals. Lasers may up-regulate skin α3β1 integrin, which in turn stimulates MAP kinase that promotes epidermal migration and inhibits epidermal hyperkeratosis. Lee *et al.* (17) reported a case series of four patients undergoing fractional carbon dioxide laser resurfacing for LS not responding to super - potent topical corticosteroids. The subjective symptoms of these four patients were improved after treatment. They found that CO_2 was clinically effective in inhibiting hyperkeratosis. The LS was subsequently able to be maintained with topical corticosteroid treatment.

Photodynamic therapy (PDT)

In recent years, PDT has been proposed as a non-invasive treatment. PDT is effective in some patients with LS, and this treatment may be considered in vulvar LS patients if topical corticosteroid treatment fails (18). According to

the 2016 European Guideline for the Management of Vulval Conditions, literature has confirmed that PDT is associated with cancers, especially those of the genital area. Thus, the long-term safety of PDT needs to be further investigated (19).

Injection of platelet-rich plasma (PRP)

Injection of PRP into vulvar lesions can promote the regeneration of normal tissues. Behnia-Willison *et al.* (20) enrolled 28 LS patients unresponsive to topical steroid treatment. The patients' own blood was centrifuged on site and injected under local anesthesia to the external genitalia. Almost all patients showed clinical improvement in the size of their lesions, and in 8 cases, lesions totally disappeared after treatment with PRP. Symptoms partially resolved in 13 patients and completely disappeared in 15 patients after treatment. The authors hypothesized that PRP is effective for treatment of LS; however, a larger pilot and/or randomized controlled trial study is required to evaluate this finding further.

Electrical stimulation of vascular smooth muscle

Electrical stimulation of vascular smooth muscle is a novel treatment for NNEDV. Studies have confirmed that bioelectrical stimulation of pelvic floor muscles (i.e., stimulation released by the electrodes placed in the perineum at different frequencies) can strengthen all the pelvic floor muscles, stimulate the dominant nerves of the pelvic floor muscles, and restore nerve function. Such effect helps to alleviate the genital itching caused by the stimulation of peripheral nerves by inflammatory mediators, thereby improving the clinical symptoms and increasing the subjective satisfaction with treatment.

Injection of adipose-derived stem cells (ADSCs)

Recent studies have emphasized that adipose tissue is a rich source of adult stem cells, i.e., the so-called adipose-derived stem cells (ADSCs). This approach uses the patient's own abundant body fat as a natural filler and avoids complications associated with foreign materials. Adipose tissue is a rich source of ADSCs. ADSCs have the ability to differentiate into a variety of cell types including adipocytes, chondrocytes, osteoblasts, and myoblasts. Therefore, they may be a promising cell therapy. Giuseppina Onesti *et al.* (21) evaluated the efficacy of ADSC-based therapy in 8 NNEDV patients; after 2 years of follow-up, a significant vulvar trophism enhancement was observed in all patients, who also reported pain reduction and sexual function improvement.

Surgical treatment

Postoperative recurrence is common among NNEDV patients, and therefore surgery is not routinely recommended. Vulvar surgery is only applied for non-neoplastic lesions in the vulvar epithelium that are accompanied by VIN or vulvar cancer. Surgical correction is feasible when the lesion causes vaginal vestibular stenosis complicated with painful intercourse or dysuria.

Psychotherapy

For long-term recurrent itching of the vulva due to non-neoplastic lesions in the vulvar epithelium, especially nighttime itching, rubbing or scratching provides immediate and temporary relief but eventually leads to thickening of the skin, which in turn leads to persistent rubbing and scratching, known as the "itch-scratch cycle". Patients are generally anxious and depressed, so it is important to assess their mental health. In patients with LSC, the mental problems often begin during the stress period and worsen as the stress level increases. Therefore, the psychological component of NNEDV must be addressed.

Summary and prospects

The exact etiology pathogenesis of NNEDV remains unclear. It may be associated with autoimmunity, local factors, heredity, infection, and hormone levels. Generally, a diagnosis of NNEDV can be made based on the clinical manifestations; however, pathological biopsy is the cornerstone for establishing a definitive diagnosis. The currently available treatments have their own advantages and disadvantages. Corticosteroid therapy is a classic clinical treatment, and more recent therapies including matrix CO2 laser resurfacing, PDT, stimulation of vascular smooth muscle, and ADSC injection have also shown good efficacy. More effective and safe approaches for NNEDV prevention and treatment are expected to occur with the advance of research in the etiology and pathogenesis of this disease.

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Footnote

Conflicts of Interest: All authors have completed the

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Lynch PJ, Moyal-Barracco M, Scurry J, et al. 2011 ISSVD terminology and classification of vulvar dermatological disorders: An approach to clinical diagnosis. J Low Genit Tract Dis 2012;16:339-44.
2. Shirer JA Jr, Ray MC. Familial occurrence of lichen Sclerosuset ayrophicas case reports of a mother and daughter. Arch Dermatol 1987;123:485-8.
3. Wei DM, Wang P, Niu XY. Epidemiology and electrophysiological therapy of vulvar dystrophies in Sichuan. Journal of Sichuan University (Medical Science Edition) 2017;48:800-3.
4. Cooper SM, Ali I, Baldo M, et al. The association of lichen sclerosus and erosive lichen planus of the vulva with autoimmune disease: a case-control study. Arch Dermatol 2008;144:1432-5.
5. Terlou A, Santegoets LA, van der Meijden WI, et al. An Autoimmune Phenotype in Vulvar Lichen Sclerosus and Lichen Planus: A Th1 Response and High Levels of MicroRNA-155. J Invest Dermatol 2012;132:658-66.
6. Higgins CA, Cruickshank ME. A population-based case-control study of aetiological factors associated with vulval lichen sclerosus. J Obstet Gynaecol 2012;32:271-5.
7. Sherman V, Mc Pherson T, Baldo M, et al. The high rate of familial lichen sclerosus suggests a genetic contribution: an observational cohort study. J Eur Acad Dermatol Venereol 2010;24:1031-4.
8. Gao XH, Bamardo MC, Winsey S, et al. The association between HLA DR, DQ antigens, and vulval lichen sclerosus in the UK: HLA DRB112 and its associated DRB112/DQB10301/04/09/010 haplotype confers susceptibility to vulval lichen sclerosus, and HLA DRB10301/04 and its associated DRB10301/04/DQB10201/02/03 haplotype protects from vulval lichen sclerosus. J Invest Dermatol 2005;125:895-99.
9. Xie L, Chang SF, Sun JC, et al. Analysis of vaginal microenvironment in 435 cases with nonneoplastic epithelial disorders of vulva. Med J Chin PLA 2016;41:136-9.
10. Gnthert AR, Faber M, Knappe G, et al. Early onset vulvar lichen sclerosus in premenopausal women and oral contraceptives. Eur J Obstet Gynecol Reprod Biol 2008;137:56-60.
11. Lee A, Bradford J, Fischer G. Evidence-based (S3) guideline on (anogenital) lichen sclerosus. J Eur Acad Dermatol Venereol 2017;31:e57-e58.
12. Bleeker MC, Visser PJ, Overbeek LI, et al. Lichen sclerosus: Incidence and risk of vulvar squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 2016;25:1224-30.
13. Lee A, Bradford J, Fischer G. Long-term management of adult vulvar lichen sclerosus: a prospective cohort study of 507 women. JAMA Dermatol 2015;151:1061-7.
14. Nguyen Y, Bradford J, Fischer G. Lichen sclerosus in pregnancy: a review of 33 cases. J Invest Dermatol 2017;137:S197.
15. Hengge UR, Krause W, Hofmann H, 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;155:1021-8.
16. Borghi A, Corazza M, Minghetti S, et al. Topical tretinoin in the treatment of vulvar lichen sclerosus: an advisable option? Eur J Dermatol 2015;25:404-9.
17. Lee A, Lim A, Fischer G. Fractional carbon dioxide laser in recalcitrant vulval lichen sclerosus. Australas J Dermatol 2016;57:39-43.
18. Lan T, Zou Y, Hamblin MR, et al. 5-Aminolevulinic acid photodynamic therapy in refractory vulvar lichen sclerosus et atrophicus: Series of ten cases. Photodiagnosis Photodyn Ther 2018;21:234-8.
19. van der Meijden WI, Boffa MJ, Ter Harmsel WA, et al. 2016 European guideline for the management

of vulval conditions. J Eur Acad Dermatol Venereol 2017;31:925-41.
20. Behnia-Willison F, Pour NR, Mohamadi B, et al. Use of platelet-rich plasma for vulvovaginal autoimmune conditions like lichen sclerosus. Plast Reconstr Surg Glob Open 2016;4:e1124.
21. Giuseppina Onesti M, Carella S, Ceccarelli S, et al. The use of human adipose-derived stem cells in the treatment of physiological and pathological vulvar dystrophies. Stem Cells Int 2016;2016:2561461.

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