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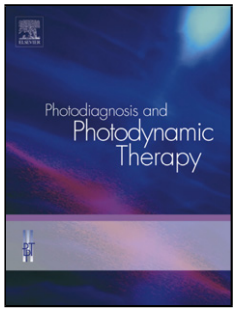

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Evaluation of the efficacy of 5-aminolevulinic acid photodynamic therapy for the treatment of vulvar lichen sclerosus

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Highlights

1.ALA-PDT is a safe and effective method for the treatment of VLS.
2.Therapeutic effects of ALA-PDT can maintain at least 3 months.
3.The therapeutic effects of ALA-PDT may reduced during 3 to 6 months.

Abstract

Background: This study aimed to evaluate the effects of 5-aminolevulinic acid photodynamic therapy (ALA-PDT) on the improvement of symptoms and recurrence rate in patients with vulvar lichen sclerosus (VLS) and observe its side effects.

Methods: The symptom scores before and after photodynamic therapy (PDT) in 13 enrolled patients with VLS were analyzed retrospectively. All patients were followed-up for at least 6 months to evaluate the recurrence rate after PDT. The

patients were treated with PDT only during the study period. During the PDT treatment, a 20% 5-aminolevulinic acid solution was applied to the lesions and marginal areas for 3 hours, and the entire area was then irradiated with 635 nm red light of 80 J/cm^2 at 80 mW/cm^2 for 30 minutes.

Results: In this study, the effective rate of PDT was 92.31%. Lesions recurred in two patients at 6 months after PDT. Post-treatment, the total subjective, total objective, and the Dermatological Life Quality Index scores changed from 11.4, 4.3, and 13.4 at baseline to 4.9, 2, and 5.9, respectively. The difference was statistically significant (p <0.05). PDT was mildly toxic in most patients.

Conclusions: ALA-PDT is a safe and effective method for the treatment of VLS, and the therapeutic effects can be maintained for at least 3 months. The therapeutic effects may decrease during the 3–6-month period after PDT.

Keywords: ALA-PDT; vulvar lichen sclerosus;

1. Introduction

Vulvar lichen sclerosus (VLS) is an incurable chronic inflammatory dermatosis [1]. VLS can affect all age groups of both sex, however, the incidence is 10 times higher in women than in men. Postmenopausal women are at a higher risk of VLS, however, younger women are also affected. The labia minora and inner aspects of the labia majora are the main sites involved in VLS.

The main symptoms of VLS are pruritus, pain, burning, and dyspareunia. VLS can eventually lead to atrophy of the labia minora, urinary obstruction, burying of the clitoris, and other dysfunctions. However, some patients are asymptomatic. VLS is a risk factor for vulvar intraepithelial neoplasia and invasive squamous cell carcinoma [2].

The pathogenesis of VLS is not known; however, some studies have reported it to be genetic-familial, which accounts for the pathogenesis in 12% of VLS cases [3–5]. It has been confirmed that human leukocyte antigen Class II antigen DQ7 is associated with the pathogenesis of VLS[6]. Patients with VLS often suffer from autoimmune diseases, such as type I diabetes, thyroid diseases, and vitiligo, indicating that VLS may be related to autoimmune disorders. The two peaks of VLS occurrence in female patients (prepuberty and postmenopausal) suggest that estrogen may play an important role in the etiology of VLS [7]. In addition, research findings have indicated an association of local and infectious factors, such as Borrelia infection, with the etiopathogenesis; however, this has not been confirmed [8].

At present, VLS remains an incurable disease. The improvement of subjective and objective symptoms is the main purpose of treatment wherein the improvement of pruritus is particularly important. Highly effective corticosteroid (0.05% clobetasol propionate) cream is the first line of treatment for VLS. Calcineurin inhibitors (CIs) are secondary treatment [9]. However,

long-term use of local corticosteroids may increase the risk of skin dryness, atrophy, and hypopigmentation [1].

In recent years, the therapeutic effect of photodynamic therapy (PDT) on VLS has attracted increasing attention. PDT plays a therapeutic role through the interaction of photosensitizing agents, oxygen, and light [10], with minimal damage to the surrounding healthy skin.

In this study, we evaluated the efficacy and safety of PDT for the treatment of VLS based on a retrospective analysis of the conditions in 13 patients with VLS who received PDT.

2. Materials and methods

2.1 Patients

We collected and evaluated clinical samples and data of 10 female patients with VLS admitted to the Department of Dermatology and Venereology, Nanfang Hospital, Southern Medical University, China, from January 2017 to January 2019.

Inclusion criteria: (1) patients had typical clinical manifestations of VLS; (2) patients had histopathological examinations showing typical VLS; (3)patients were older than 18 years; (4) patients had approved PDT and were followed up for at least 6 months; (5) patients did not use corticosteroids or drugs affecting immune function 3 months before receiving PDT.

Exclusion criteria: (1) patients hadhuman papillomavirus, fungal or bacterial infections of the vulva; (2) patients had genital tumors or precancerous lesions of the vulva, vagina, or uterus; (3) patients were pregnant or lactating; (4) patients had been treated with local corticosteroids during PDT and follow-up; (5)patients had received systematic hormone therapy.

All patients voluntarily received PDT and signed the informed consent forms. This study was approved by the Nanfang Hospital Ethics Committee.

2.2 Photodynamic therapy

In this study, PDT combined with 5-aminolevulinic acid (ALA) (Fudan Zhangjiang Bio-Pharm Co. Ltd, Shanghai, China) was used to treat patients with VLS. A solution of 20% 5-ALA was prepared in 0.9% aseptic sodium-chloride solution before treatment.

Therapeutic procedures were as follows: (1) We covered the lesion and margins (radius 1 cm) with cotton soaked in 20% 5-ALA solution, and then put a plastic film and surgical gauze over the cotton to promote better absorption of the 5-ALA solution and prevent its loss. (2) We kept the lesions and marginal areas in full contact with the 20% 5-ALA solution for 3 hours. (3) We then removed the plastic film and surgical gauze and used the red light of 635 nm of 80 J/cm^2 at 80 mW/cm^2 emitted by semiconductor laser (LD 600 C, Wuhan Yage Optic and Electronic Technique Co., Ltd., Wuhan, China) to irradiate the

lesion area and margins for 30 minutes. There was no need for anesthesia. PDT was applied once a week. Patients were advised to empty their bladders before treatment and avoid drinking water or urinating during treatment. Depending on their condition, the patients were treated with PDT four to nine times. They were followed up for at least 6 months after PDT at follow-up intervals of 3 and 6 months.

2.3 Assessment

The objective and subjective scoring criteria in this study are based on a study by Borghi, et al [11–15]. A visual analogue scale (VAS 0～10) was used to evaluate the subjective symptoms of pruritus, burning, and pain, with 0 representing asymptomatic and 10 maximum sensory intensity. The total subjective score (TSS) was obtained by summing the three subjective symptom scores. The objective parameters included: (1) leukoplakia, (2) erythema, (3) hyperkeratosis, and (4) purpuric lesions and itching-related excoriations. We scored the four objective parameters and the severity of the symptoms was graded as: 3 = severe, 2 = moderate, 1 = mild, 0 = absent. The total objective score (TOS) was obtained by summing the four objective parameter scores. The highest scores of TSS and TOS were 30 and 12, respectively. Subjective and objective scores were obtained before PDT, after PDT, and 3 and 6 months after PDT. After PDT, each subjective symptom score ≤3 and TOS ≤4 were considered significant. Recurrence was defined as at least one subjective

symptom score ≥ 5, an objective parameter score = 3 or a sclerosing lesion showing increased symptoms. The Dermatological Life Quality Index (DLQI) score was used to evaluate all patients before and after PDT. The Female Sexual Function Index (FSFI) score was used to evaluate the sexual function of the patients. The objective parameter scores were evaluated by two researchers.

2.4 Statistical analysis

SPSS Statistical 19.0 was used to analyze the data. The subjective, objective, and DLQI scores before and after PDT were analyzed by Wilcoxon's test. $p<0.05$ was considered to be statistically significant.

3. Results

3.1 Patient baseline characteristics

We enrolled 10 female patients with VLS. The baseline characteristics are shown in Table 1. No patients suffered from autoimmune diseases, such as diabetes, thyroid diseases, vitiligo, alopecia areata, and pernicious anemia. No patients had a family history of VLS. Eight patients (80%) had a history of topical corticosteroid treatment with unsatisfactory results.

3.2 Efficacy evaluations

After PDT, all patients met the criteria for effective treatment. There was no recurrence at 3 months after PDT. Recurrence was observed in 2 patients (20%) at 6 months after PDT. Table 2 shows the scores of the patients before

and after treatment and during follow-up. PDT significantly improved the subjective and objective symptoms of the patients. The average TSS of the patients before treatment was 11.4, which decreased to 4.9 after PDT (p = 0.008). As one of three subjective symptom scores, the pruritus score also decreased significantly from 4.8 to 2 (p = 0.007). After PDT, the average TOS of the patients decreased from 4.3 to 2, which was also statistically significant (p = 0.005). There were no significant differences in mean TSS and TOS three months after PDT compared with those after PDT (p = 0.083, p = 0.317). Mean TSS and TOS 6 months after PDT were higher than those after PDT (p = 0.010, p = 0.014). However, the mean TSS and TOS scores 6 months after PDT were significantly lower than those at baseline (p = 0.007, p = 0.004). Patients (5/10) marked NA in the FSFI column were not sexually active during the follow-up period. According to the numerical trend (not statistical analysis) of patients not marked NA, the FSFI scores improved after PDT. The DLQI score decreased from 13.4 at baseline to 5.9 (p = 0.005), and the FSFI score from 8.5 to 17.67 (p = 0.027). None of the patients showed any deterioration of VLS after PDT. The number of patients whose TSS, TOS, pruritus, and DLQI scores improved ≥50% after PDT were 7, 7, 7 and 7, respectively.

3.3 Adverse reaction

Eight patients (80%) complained of mild to moderate pain during PDT. However, no patients requested an interruption of PDT due to pain. Local

burning sensation, edema, and erythema occurred in 6 patients (60%) after PDT, which subsided within 5 days after treatment. No blisters, pigmentation, erosion, necrosis or other symptoms occurred in the patients. No systemic adverse reactions occurred in the patients.

4. Discussion

VLS severely impacts the physical and mental health of patients because of its obstinate vulvar pruritus, dyspareunia, and other symptoms, as well as irreversible vulvar atrophy, burying of the clitoris, and other sequelae. Due to its distinct location and diagnostic negligence, the incidence of VLS may be higher than the currently reported 1.7% (among women undergoing general gynecological examinations)[16]. A study by Lee A, et al. indicated that the early intervention of VLS can prevent vulvar atrophy, scarring, deformation and carcinogenesis [17]. Early diagnosis and reasonable treatment are particularly important to VLS patients.

At present, PDT is widely used in the treatment of condyloma acuminatum, Bowen's disease, psoriasis, basal cell carcinoma, and other non-melanoma skin diseases [18]. PDT is increasingly recognized as a non-invasive therapy for VLS [10]. The exact mechanism of PDT in the treatment of VLS is unclear. According to the existing literature, PDT can regulate the immune function of local cells and affect the immune response of the body [19]. Some studies have demonstrated that PDT can produce cytotoxic reactive oxygen species through

photochemical action to kill proliferating cells and induce local T lymphocyte apoptosis [18]. It can also promote local skin microcirculation to improve skin lesions. PDT can restore skin elasticity by increasing the production of type Ⅰ and Ⅲ procollagen, thus facilitating dermal remodeling, and increasing epidermal thickness and collagen density [20]. The above regulatory mechanisms may be involved in the treatment of VLS with PDT.

In this study, PDT is effective for all patients, and there was recurrence in two patients at 6 months after PDT. PDT significantly relieved the subjective and objective symptoms of the VLS in patients and improved their quality of life. This is similar to Maździarz's findings; however, in contrast, Imbernón-Moya's study shows that PDT does not improve objective symptoms [21, 22]. The improvement of pruritus was the most significant.In addition, our study showed that PDT may improve sexual function in VLS patients. In Figure 2, patients (5/10) marked NA in the FSFI column were not sexually active during the follow-up period. Therefore, this index was not statistically analyzed and only the trend of FSFI scores before and after PDT were observed. Most of the patients experienced mild local toxicity induced by PDT which may be related to the private site of VLS, red light source, and irradiation time and intensity. However, this toxicity disappeared within a week. There were no systemic side effects in all patients. It is important to note that most patients in our study (9/10) were aged <50 years, which was not

consistent with the previously reported highest VLS prevalence in women aged >50 years: This may be because patients of child-bearing age are more likely to receive higher cost PDT treatment; this group of patients may have better economic status, more needs of sex and bearing requirements.

Although PDT can maintain the integrity of the vulvar structure compared with the surgical treatments [10], it cannot restore atrophied structures, such as the labia minora. The therapeutic effects of inhibiting precancerous lesions and tumors may reduce the possibility of malignant transformation of VLS. Furthermore, PDT may be less effective in patients with older age, longer history of VLS, and more severe atrophy.

At present, there is no standard protocol for PDT for the treatment of VLSas shown in Supplementary Figure 1. Based on the available literature and our clinical experience, we generally recommend that VLS patients receive 6 to 9 rounds of PDT. We recommended 9 rounds of PDT for patients who had already developed labia minora atrophy or burying of the clitoris and 6 rounds for other patients. In previous studies, the concentration of the photosensitizer, the wavelength of the light source, the number of rounds of PDT, and interval of treatment sessions vary, thus the final therapeutic effects also vary [10].

The perineum is particularly sensitive to pain and, as such, pain is the main side effect of PDT. As irradiation intensity is the main influencing factor on the degree of pain, in order to reduce the degree of pain and provide the same

curative effect for patients, the fluence rate of PDT can be reduced and the irradiation prolonged [23, 24].

In conclusion, this study proved that ALA-PDT is a safe and effective method for the treatment of VLS. The treatment can improve the subjective and objective symptoms of VLS patients and the therapeutic effect could be retained at least 3 months after PDT, although the symptoms may recur after 3 months. Because of the small number of patients in our study, it is necessary to further expand the sample size and set up a clobetasol propionate group to support the aforementioned conclusions. It will also be helpful to further analyze the curative effects of PDT by increasing the sample size to include postmenopausal patients and those of child-bearing age [25, 26]. Moreover, it will be beneficial to further investigate the curative effect of different PDT treatment methods and combination treatments, such as with topical corticosteroid ointments, to obtain an optimized treatment protocol.

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Ethical approval: This study was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University.

Conflicts of Interest: None

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Figure Legends

Figure 1.

Therapeutic procedures

A: The lesions and margins (radius 1 cm) are covered with cotton soaked in 20% 5-ALA, and then a plastic film and surgical gauze are placed over the cotton to promote better absorption of 5-ALA and prevent its loss.

B: The lesions and marginal areas are kept in full contact with a solution of 20% 5-ALA for three hours.

C: The gauze and film layer is removed and red light of 635 nm of 80 J/cm^2 at 80 mW/cm^2 emitted by a semiconductor laser (LD 600 C, Wuhan Yage Optic and Electronic Technique Co., Ltd., Wuhan, China) is used to irradiate the lesion area and margins for 30 minutes.

5-ALA: 5-aminolevulinic acid

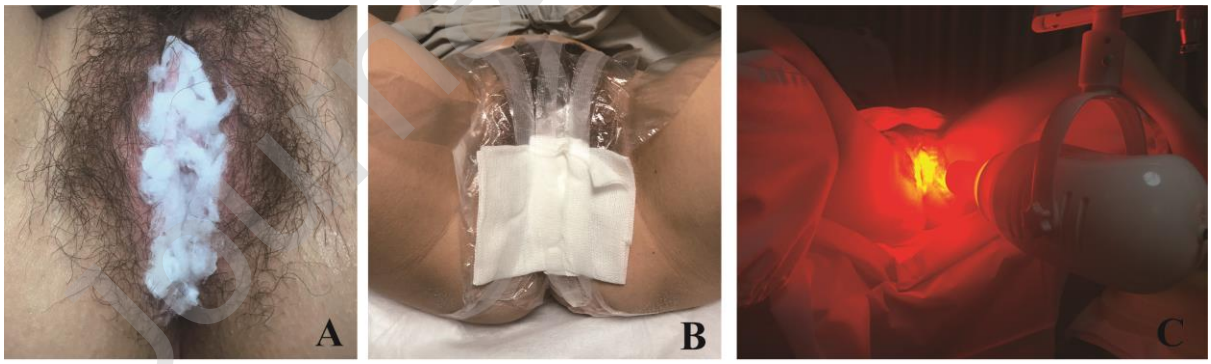

Figure 2.

Pre and post treatment images of patient No. 12

A: Before PDT

B: After the last PDT session

C: 3 months after the last PDT session

D: 6 months after the last PDT session

PDT: photodynamic therapy

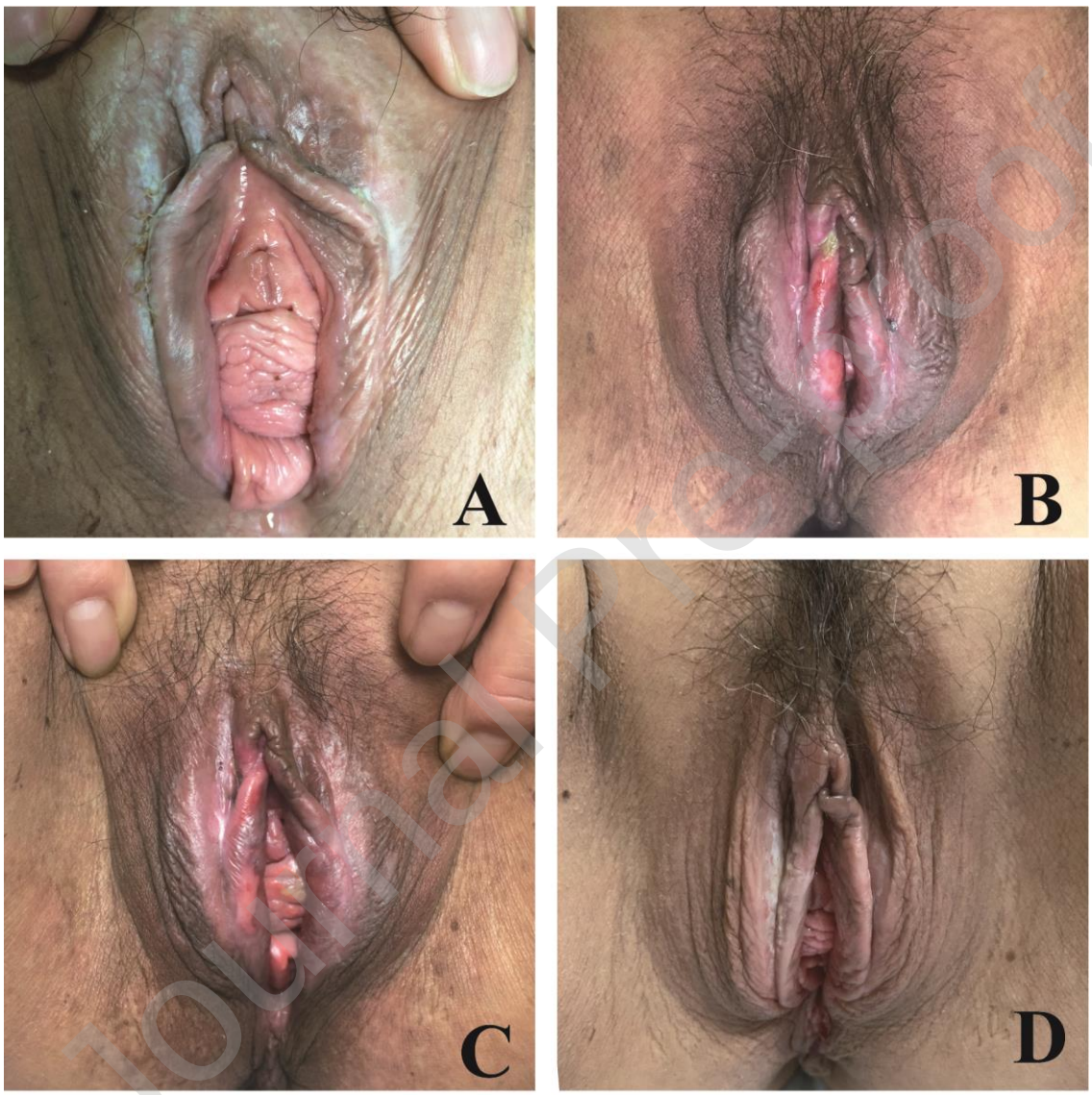

Table 1 Patient baseline characteristics

Characteristic	Value
Age, years, mean ± SD, (range)	35.4±11.73
Onset age, years, mean ± SD, (range)	33.8±11.96
Disease duration, years, mean ± SD, (range)	1.63±0.79
Diagnostic delay, months, mean ± SD, (range)	7.6±4.53
Primary ;recurrence cases, n	2:8
Patients who have received medication,n,(%)	8 (80 %)

Table 2 Symptom scores in VLS patients treated with PDT

Patients no./ age (years)	PDT sessions	TSS before PDT	TSS after PDT	TSS 3 months	TSS 6 months	TOS before PDT	TOS after PDT	TOS 3 months	TOS 6 months	Pruritus before/after PDT	DLQI before/after PDT	FSFI before/after PDT
1/24	6	18	9	9	10	4	2	2	3	5/3	18/10	NA
2/34	9	18	3	4	8	6	3	3	4	7/1	20/4	3/15
3/28	6	9	5	5	6	2	0	0	1	4/2	12/6	7/20
4/18	6	9	3	3	4	3	2	2	2	5/1	10/2	NA
5/38	6	10	4	4	5	3	2	2	2	6/2	15/5	12/22
6/42	6	12	7	8	8	6	2	3	3	6/3	14/8	10/16
7/41	6	13	6	6	8	6	3	3	3	5/3	13/10	8/18
8/57	6	16	7	8	12	5	2	2	3	7/3	20/10	NA
9/46	6	9	5	5	5	3	2	2	2	3/2	8/3	11/15
10/26	6	0	0	0	0	5	2	2	3	0/0	4/1	NA
Mean± SD		11.4 ±5.38	4.9± 2.56	5.2± 2.70	6.6± 3.37	4.3± 1.49	2± 0.82	2.1± 0.88	2.6± 0.84	4.8±2.10/2±1.05	13.4±5.19 /5.9±3.45	8.5±3.27/ 17.67 ±2.88

VLS, vulvar lichen sclerosus; PDT, photodynamic therapy; TSS, total subjective score; TOS, total objective score; LQI, Dermatological Life Quality Index; FSFI, Female Sexual Function Index; NA,not applicable.