Photodiagnosis and Photodynamic Therapy 19 (2017) 135–139

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Photodynamic therapy in the treatment of vulvar lichen sclerosus☆

Agnieszka Maździarz*, Beata Osuch, Magdalena Kowalska, Agnieszka Nalewczyńska, Beata Śpiewankiewicz

Department of Gynecologic Oncology, The Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Warsaw, Roentgena Street 5, 02-781 Warsaw, Poland

ARTICLE INFO

Keywords:
Lichen sclerosus
Photodynamic therapy
PDT
Aminolevulinic acid
ALA
Vulvoscopy

ABSTRACT

Background: Vulvar lichen sclerosus is a chronic and incurable disease that causes various unpleasant symptoms and serious consequences.
Objective: The purpose of the study was to assess the effectiveness of photodynamic therapy in the treatment of vulvar lichen sclerosus.
Methods: Participants in the study included 102 female patients aged 19–85 suffer from vulvar lichen sclerosus. The patients underwent photodynamic therapy (PDT). In the course of PDT the 5% 5- aminolevulinic acid was used in gel form. The affected areas were irradiated with a halogenic lamp PhotoDyn 501 (590–760 nm) during a 10-min radiation treatment. The treatment was repeated weekly for 10 weeks.
Result: PDT has brought about a good therapeutic effect (complete or partial clinical remission), with 87.25% improvement rate in patients suffering from lichen sclerosus. The greatest vulvoscopic response was observed in the reduction of subepithelial ecchymoses and teleangiectasia (78.95%), and the reduction of erosions and fissures (70.97%). A partial remission of lichenification with hyperkeratosis was observed in 51.61% of cases. The least response was observed in the atrophic lesions reduction (improvement in 37.36% of cases).
Conclusion: Our patients suffering from vulvar lichen sclerosus demonstrated positive responses to photodynamic therapy and the treatment was well tolerated. Photodynamic therapy used to treat lichen sclerosus yields excellent cosmetic results.

1. Introduction

Lichen sclerosus (LS) of the vulva is a chronic dermatosis of atrophic inflammatory character, accompanied by a lymphocytic response [1,2].

Most frequently (in 85–98% of the cases) LS occurs in the area of external genitalia and the anus. In 15–20% of the cases LS occurs in other (not genital) parts of the body: on the skin of the upper torso, in the armpits, as well as on the buttocks and thighs [3]. Women suffer from LS ten times more often than men do. LS affects all age groups, with an increased frequency in post-menopausal women [4]. However, as much as 10% of all cases occurs in children under six years of age. LS usually causes many chronic ailments and conditions [3,4].

The etiology of this disease has not yet been fully explained. Among a plethora of pathogenic factors mentioned in literature, the most likely source of LS is autoimmunologic and genetic. This hypothesis is proved by a more frequent occurrence of tissue-specific antibodies, co-existence of LS with other autoimmunologic diseases, in particular autoimmune thyroid disease and vitiligo, as well as associations with the HLA class II antigene DQ7 [3–5]. LS is a chronic and incurable disease [4]. Treatment usually leads to improvement, which can be temporary, but there can be times when treatment does not bring desired results (Figs. 1–3).

2. Materials and methods

Participants in the study included 102 female patients aged 19–85 (the average age was 55.08), who were undergoing treatment for LS in the Department of Oncological Gynecology at the Oncology Center in Warsaw, Poland, in 2012–2014. Each patient underwent a biopsy of the vulva; following histopathology, LS was diagnosed.

Prior to the study, all patients had been qualified for treatment with clobetasol propionate (0.05% ointment). However, for a variety of reasons this therapy did not bring expected outcomes, or the patients did not agree to being treated with steroids. In both cases the patients

Abbreviations: LS, lichen sclerosus; ALA, 5 - aminolaevulinic acid; PDT, photodynamic therapy; DMSO, dimethyl sulfoxide; MAL, methyl ester of aminolevulinic acid, methyl aminolevulinate; LED, light-emitting diode; PpIX, protoporphyrin IX; VIN, vulvar intraepithelial neoplasia

☆ The material contained in the manuscript has not been published, has not been submitted for publication.

* Corresponding author.
E-mail addresses: agaem855@interia.pl (A. Maździarz), ginonkol@coi.waw.pl (B. Śpiewankiewicz).

http://dx.doi.org/10.1016/j.pdpdt.2017.05.011
Received 26 February 2017; Received in revised form 29 April 2017; Accepted 14 May 2017
Available online 17 May 2017

Fig. 1. Vulvar lichen sclerosus. Vuvoscopy of 3 patients before treatment showing lichenification with (A) hyperkeratosis, (B) atrophic lession with fissure, (C) telangiectases and ecchymosis.

were included in the study – photodynamic therapy (PDT).

In the course of PDT the 5% 5 - aminolevulinic acid (ALA) was used in gel form, with the 2% concentration of DMSO (dimethyl sulfoxide). The photosensitizer had been prepared by Prof. Alfreda Graczyk in the Department of Optoelectronics of the Military Technical Academy in Warsaw, Poland, with the collaboration of the pharmaceutical company Farmapol. The gel was then applied to the vulva. After three hours the affected areas were irradiated with a halogenic lamp PhotoDyn 501 (590–760 nm) with power density of 204 mW/cm^2, which generates a dose of 120 J/cm^2 during a 10-min radiation treatment. The treatment was repeated once-a-week for 10 weeks.

The assessment of effectiveness of PDT was performed three months after the completion of the therapy. During this follow-up visit patients were asked to evaluate the effectiveness of the photodynamic therapy by choosing one of five possible answers:

1. I am very satisfied. I do not experience any discomfort, or I experience it sporadically. Photodynamic therapy helped me 100–70%.
2. I am satisfied. My improvement rate is around 50%. Photodynamic therapy helped me 50%.
3. I feel some improvement. Photodynamic theraphy has helped me 30%.
4. I am not satisfied. I do not feel any improvement, or my improvement is less than 30%. Photodynamic therapy has not helped me.
5. My condition has worsened after photodynamic therapy.

In addition to the aforementioned verbal self-assessment, we performed a vulvoscopic evaluation of treatment. All patients underwent vulvoscopy. A colposcope PZO Klp 21 was used; it provided images at the 3×, 5×, 8×, 12×, and 20× magnification levels. The following characteristics of the vulvoscopic image were taken into consideration:

1. Lichenification with hyperkeratosis
2. Atrophic lessions
3. Subepithelial ecchymoses and teleangiectases
4. Erosions and fissures
5. Suspicion of VIN or cancer, determined by vulvoscopy

The post-treatment follow-up continued for twelve months; the visits were performed after six and twelve months since treatment.

The study and treatment were approved by the Bioethics Committee at the Oncology Center-The Marie Skłodowska-Curie Institute in Warsaw, Poland (approval certificate 1/2012).

3. Results

The study group consisted of 102 female patients aged 19–85 (on average 55.08 years old). The patients suffered from LS for the duration of 1–29 years (on average 4.59 years).

76 patients (74.50%) were post-menopausal. Menopause took place on average at 50.9 years of age.

32 patients (31.37%) suffered from other autoimmunologic disorders in addition to LS. Table 1 shows the autoimmunologic diseases that accompanied LS in the study sample.

To participate in the study we chose patients who were originally qualified for the clobetasol propionate treatment for the period of one year preceding the study, and whose therapy did not bring desired results: 38 patients used clobetasol and achieved a partial remission of disease, but overall they were not satisfied with the final outcome. 15 patients stopped treatment due to the worsening of their symptoms or inflammation. 49 patients refused to use topical corticosteroids. All those patients were qualified for photodynamic therapy (PDT). A probable reason for why a large number of patients did not benefit from the treatment with corticosteroids, is that the Department of Gynecologic Oncology (The Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Warsaw) accepts patients from across the nation, who also suffer from other ailments and

Fig. 2. Fig. 1. Vulvar lichen sclerosus. Vulvoscopy of patient showing lichenification with hyperkeratosis before photodynamic therapy: (A) vulva (B) clitoris and (C) perineum.

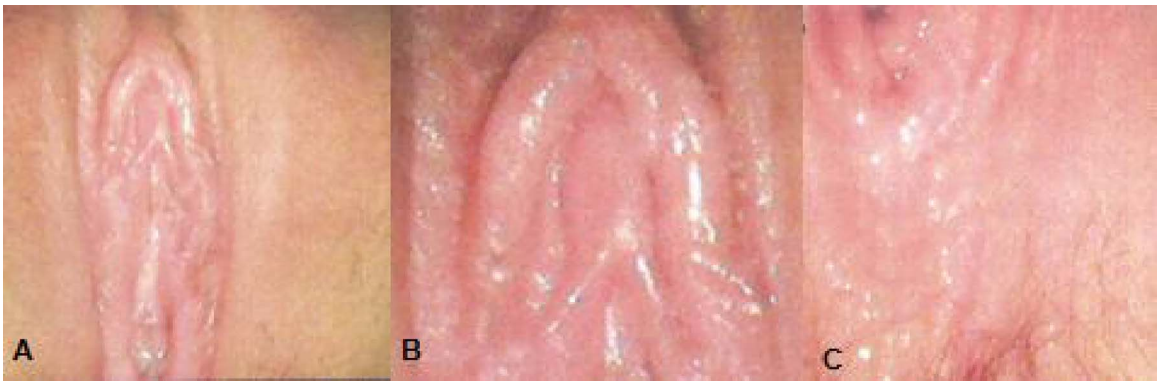

Fig. 3. Vulvar lichen sclerosus. Vulvoscopy of the same patient as in Fig. 2 after photodynamic therapy showing significant improvement in lichenification with hyperkeratosis: (A) vulva (B) clitoris and (C) perineum.

Table 1
Autoimmunologic diseases accompanying LS.

Autoimmunologic disease accompanying LS	Number of affected patients (%)
Hashimoto's thyroiditis	22 (21.57%)
Systemic lupus erythematosus	5 (4.90%)
Vitiligo	4 (3.92%)
Sjögren's syndrome	1 (0.98%)
Total	32 (31.37%)

complications resistant to treatments.

One cycle of PDT included ten courses at seven-day intervals. During the therapy 39 (38.24%) patients experienced paresthesia (a sensation of "pins and needles" in the treated area). In 12 (11.76%) patients we observed swelling that subsided after a few hours. In both cases the discomfort was minor and patients were not given any medications. No patient declined further treatment. All patients completed the entire cycle of ten PDT courses. Photodynamic therapy did not cause the condition of any patient to deteriorate. Follow-up was continued for twelve months (three control visits total, at three, six, and twelve months).

After three months a thorough assessment of the effectiveness of therapy was performed. The basis for the assessment was a subjective evaluation by patients who were asked to choose one of five possible answers to a question they were asked: "What is the degree of effectiveness of the photodynamic therapy in the treatment of my symptoms connected with LS?" Table 2 shows the results of the assessment.

A complete or partial remission was achieved in 87.25% (89 patients). Photodynamic therapy did not help 12.75% (13 patients), who were offered a different treatment.

During the three-month check-up the effectiveness of photodynamic therapy was assessed via vulvoscopy. The results of vulvoscopy are presented in Table 3. The observation showed that the final result of treatment can be assessed after 3 months, most likely because photodynamic reactions need that length of time to be finalized. Therefore the first assessment of the treatment results was done after 3 months.

The greatest vulvoscopic response was observed in the reduction of subepithelial ecchymoses and teleangiectasies (78.95%) same as reduction of erosions and fissures (70.97%). A partial remission of lichenification with hyperkeratosis was observed in 51.61% of cases. The least response was observed in the atrophic lessions reduction (37.36% of cases).

At the 12-month check-up, vulvoscopic assessment did not show any cases of disease progression or transformation into VIN or cancer. 17 patients missed their check-ups. Auxiliary treatment in the form of emollients applied topically, was provided during the 12-month observation period in the case of patients who had not been completely satisfied with the PDT treatment results. Corticosteroids were not used during the twelve-month observation of patients.

4. Discussion

Lichen sclerosus of the vulva may have various unpleasant symptoms, such as itching, pain, and burning. In the aftermath of progressing atrophic lesions and scarring, with time, dyspaurenia can develop. The main causes of dyspaurenia include chafing, erosions, and narrowing of the vagina opening. These ailments and sex life issues, which accompany LS, significantly deteriorate quality of life in patients [3].

Macroscopy shows white, wax-like, multi-sided papules, which merge into shiny bundles, present in the epithelium affected by LS. The skin is thin and atrophic. Erosions and tearing appear, mainly in the area of the commissure of the inner labia and around the anus. If the disease lasts for many years, it causes progressive scarring that leads to the disintegration of the vulvar structures [3,4,6].

Microscopic characteristics vary according to the disease stage at the moment of biopsy. Changes typical for LS include hyperkeratotic epithelium, epidermal atrophy with loss of rete Bridges, hydropic degeneration of the basal layer or mild spongiosis, with subepithelial sclerotic collagen and lymphatic infiltrate in the dermis [3,7].

There is a risk of malignant transformation in the areas affected by LS, but the risk rate is less than 5%. In such cases it is squamous cell carcinoma and verrucous carcinoma that develop most frequently [4]. Therefore patients who suffer from LS require strict gynecologic care. If suspect changes are detected in the course of a clinical or vulvoscopic exam, a repeat biopsy and histopathological verification are required.

In the past LS was treated with keratolytic compounds, alkalis,

Table 2
Patients' assessment of the effectiveness of photodynamic therapy in the treatment of symptoms connected with LS of the vulva.

Patients' assessment of the effectiveness of photodynamic therapy as related to the intensity of symptom/discomfort	Number of patients (%)
1. I am very satisfied. I do not experience any discomfort, or I experience it sporadically. Photodynamic therapy helped me 100-70%.	62 (60.78%)
2. I am satisfied. My improvement rate is around 50%. Photodynamic therapy helped me 50%.	17 (16.67%)
3. I feel some improvement. Photodynamic therapy has helped me 30%.	10 (9.80%)
4. I am not satisfied. I do not feel any improvement, or improvement less than 30%. Photodynamic therapy has not helped me.	13 (12.75%)
5. My condition has worsened after photodynamic therapy.	0
Total	102 (100%)

Table 3
Comparison of the results of vulvoscopy regarding the presence of LS before treatment and after PDT.

Characteristics of the vulvoscopic image	Total number of patients before PDT, with significant LS characteristics shown via vulvoscopy (100%)	Number of patients post therapy, with any regression shown via vulvoscopy (%)	Number of patients whose LS stabilized, as shown via vulvoscopy (%)
Lichenification with hyperkeratosis	93	48 (51.61%)	45 (48.39%)
Atrophic lessions	91	34 (37.36%)	57 (62.64%)
Subepithelial ecchymoses and teleangiectases	19	15 (78.95%)	4 (21.05%)
Erosions and fissures	62	44 (70.97%)	18 (29.03%)
Suspicion of VIN or cancer, as determined by vulvoscopy	0	0	0

exfoliants, testosterone, progesterone, and estrogens, as well as antimalaric oral medications [4]. Historically, radiotherapy was used in the treatment of LS, too, as were various surgical procedures resulting in partial or total excisions of the vulva [6]. However, the relapse rate following these types of treatment was exceptionally high at 85% [6,8].

Currently, the first-line treatment involves applying corticosteroids topically, first and foremost clobetasol propionate 0,05% [3]. The cream should be applied once daily in the evening for four weeks, followed by an application every second day for the following four weeks, and ending with an application twice or thrice weekly for the following four weeks [3,4]. Topical steroid is an effective treatment for vulvar lichen sclerosus [9,10]. However, prolonged topical steroid treatment may result in various side effects, such as the thinning of the dermis, systemic absorption, striae formation, and fungal infections. These conditions occur rarely but the risk of their occurrence exists, and therefore following the treatment regime faithfully is of utmost importance [11].

In the second-line treatment, particularly if no improvement has been observed, 0.1% tacrolimus and 1% pimecrolimus can be used [2]. 101. Nonetheless, a long-term safety profile of these medications in the LS treatment is not fully agreed upon yet [1,12].

Photodynamic therapy is yet another kind of available treatment, one that is based on the interaction of light, oxygen, and a photosensitizer. PDT is based on photocytotoxic reactions which cause the destruction of cellular structures in the pathologically altered area. PDT involves applying the photosensitizer in the affected area, followed by irradiation of this spot with light, which initiates toxic photochemical reactions. Currently, the 5 - aminolaevulinic acid (ALA) or its methyl ester (MAL) is used in the treatment of surface skin lesions [13–15]. ALA is the protoporphyrin IX (PpIX) precursor. In the affected tissue PpIX is collected selectively as a result of inefficient enzymatic pathways.

In our study the 5% 5-delta aminolevulinic acid (ALA) was used in gel form, with the 2% concentration of dimethyl sulfoxide (DMSO). The addition of DMSO facilitates and speeds up transportation (absorption) of the ALA to the deeper layers of skin, which increases the effectiveness of therapy. This was our only reason for using DSMO. We can only speculate as to possible other positive uses of DSMO in the treatment of patients. The concentration of DSMO we used – 2% – was very low; therefore it is improbable that DSMO was an active factor in treating lichen sclerosus. Effective medications, which contain the compound, have much higher concentrations of DSMO. Theoretically DSMO could have analgesic and pain-relieving properties. DSMO would then alleviate symptoms of lichen sclerosus and would support photodynamic therapy, which would also be desirable, since patients would feel more comfortable and would tolerate treatment better [16].

Usually red light 635 nm in wavelength, with the depth of penetration 8–10 mm, is used [13–15]. Lasers are ideal sources of light in PDT, but they are very expensive. Therefore alternative sources of light are frequently used, such as the light-emitting diodes (LEDs) or halogen lamps [17,18].

Patients usually tolerate PDT well; reported side effects have been associated with treatment protocols, mainly the type of light used and the duration of irradiation. Among our patients we have not noticed any significant side effects. 38,24% patients complained of a paresthesia, in the irradiated area, which stopped when the irradiation process ended (this lasted for about a few minutes). Paresthesia observed at the time of photodynamic treatment was temporary and ended when the photodynamic therapy sessions were finished. Paresthesia was usually observed only during the first 2–3 sessions.

The mechanism responsible this reaction is not clear. A possible explanation might be the phenomenon of hyperthermia in the irradiated tissues or an effect of a photochemical reaction [19,20]. Immediately after the treatment there might appear slight erythema or edema, both of which resolve spontaneously and do not require further treatment. We did not observed any allergic reaction caused by the used photosensitizer or treatment procedure.

Cosmetic results are excellent. Photodynamic therapy does not cause scarring, and therefore relatively large affected areas can be treated in a non-invasive way. PDT has brought about a good therapeutic effect, with the 87.25% improvement rate in patients suffering from lichen sclerosus. This rate is similar to the rate reported by other researchers [15] and it is comparable to the improvement rates when patient have been treated with steroids or pimecrolimus [10,21]. The most important thing is that in the LS therapy, the treatment should decrease the risk of cancerous transformations [21,22]. Photodynamic therapy meets this expectation. PDT is also an oncological therapy that can be used in treating pre-malignant lesions and malignant cancers. Therefore PDT can be considered as a well tolerated therapy that can be used effectively to treat lichen sclerosus, alongside other methods.

5. Conclusions

1. Our patients suffering from vulvar lichen sclerosus demonstrated positive responses to photodynamic therapy and the treatment was well tolerated.
2. Photodynamic therapy used to treat lichen sclerosus yields excellent cosmetic results.

Conflicts of interest

The authors have no conflict of interest to declare.

Funding

This article has no funding source.

References

[1] S.M. Neill, F.M. Lewis, F.M. Tatnall, et al., British Association of Dermatologists' guidelines for the management of lichen sclerosus, Br. J. Dermatol. 163 (2010) (2010) 672–682.
[2] S. Kauppila, V. Kotila, E. Knuuti, et al., The effect of topical pimecrolimus on inflamatory infiltrate in vulvar lichen sclerosus, Am. J. Obstet. Gynecol. 202 (2010) 181–184.
[3] V. Monsálvez, R. Rivera, F. Vanaclocha, Lichen sclerosus, Actas Dermosifiliogr. 101

(2010) 31–38.
[4] C.C. Chi, G. Kirtschig, M. Baldo, F. Lewis, S.H. Wang, F. Wojnarowska, Systematic review and meta-analysis of randomized controlled trials on topical interventions for genital lichen sclerosus, J. Am. Acad. Dermatol. 67 (2012) 305–312.
[5] S.M. Cooper, I. Ali, M. Baldo, F. Wojnarowska, The association of lichen sclerosus and erosive lichen planus of the vulva with autoimmune disease: a case–control study, Arch. Dermatol. 144 (2008) 1432–1435.
[6] R. Kunstfeld, R. Kirnbauer, G. Stingl, et al., Successful treatment of vulvar lichen sclerosus with topical tacrolimus, Arch. Dermatol. 139 (2003) 850–852.
[7] L.J. Burrows, H.A. Shaw, A.T. Goldstein, The vulvar dermatoses, J. Sex. Med. 5 (2008) 276–283.
[8] L. Edwards, Diseases and disorders of the anogenitalia of females, in: I.M. Freedberg, A.Z. Eisen, K. Wolff, et al. (Eds.), Fitzpatrick's Dermatology in General Medicine, 5th ed., McGraw-Hill, New York, NY, 1999, pp. 1377–1396.
[9] S.M. Cooper, X.H. Gao, J. Powell, et al., Does treatment of vulvar lichen sclerosus influence the prognosis? Arch. Dermatol. 140 (2004) 702–706.
[10] C. Renaud-Vilmer, B. Cavelier-Balloy, R. Porcher, L. Dubertret, Vulvar lichen sclerosus: effect of long-term topical application of a potent steroid on the course of the disease, Arch. Dermatol. 140 (2004) 709–712.
[11] A.T. Goldstein, A. Creasey, R. Pfau, D. Phillips, L.J. Burrows, A double – blind, randomized controlled trial of clobetasol versus pimecrolimus in patients with vulvar lichen sclerosus, J. Am. Acad. Dermatol. 64 (2011) 99–104.
[12] G. Fischer, J. Bradford, Topical immunosuppressants, genital lichen sclerosus and the risk of squamous cell carcinoma, J. Reprod. Med. 52 (2007) 329–331.
[13] K.A. Salva, Photodynamic therapy: unapproved uses dosages, or indications, Clin. Dermatol. 20 (2002) 571–581.
[14] L.R. Braathen, R.M. Szeimies, N. Basset-Seguin, et al., Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus, J. Am. Acad. Dermatol. 56 (2007) 125–143.
[15] A.A. Zawislak, W.G. McCluggage, R.F. Donnelly, P. Maxwell, J.H. Price, S.P. Dobbs, H.R. McClellan, A.D. Woolfson, P.A. Mccarron, Response of vulval lichen sclerosus and squamous hyperplasia to photodynamic treatment using sustained topical delivery of aminolevulinic acid from a novel bioadhesive patch system, Photodermatol. Photoimmunol. Photomed. 25 (2009) 111–113 for photodynamic therapy.
[16] K. Capriotti, J.A. Capriotti, Dimethyl sulfoxide. History, chemistry, and clinical utility in dermatology, J. Clin. Aesthet. Dermatol. 5 (2012) 24–26.
[17] L. Brancaleon, H. Moseley, Laser and nonlaser light sources, Lasers Med. Sci. 17 (2002) 173–186.
[18] A. Juzeniene, P. Juzenas, L.W. Ma, V. Iani, J. Moan, Effectiveness of different light sources for 5-aminolevulinic acid photodynamic therapy, Lasers Med. Sci. 19 (2004) 139–149.
[19] D.K. Kelleher, J. Bastian, O. Thews, P. Vaupel, Enhanced effects of aminolaevulinic acid-based photodynamic therapy through local hyperthermia in rat tumours, Br. J. Cancer 89 (2003) 405–411.
[20] Y.N. Chaves, L.A. Torezan, A.B. Niwa, et al., Pain in photodynamic therapy: mechanism of action and management strategies, An. Bras. Dermatol. 87 (2012) 521–526.
[21] J. Bradford, G. Fischer, Long – term management of vulval lichen sclerosus in adult women, Aust. N. Z. J. Obstet. Gynaecol. 50 (2010) 148–152.
[22] S.K. Fistarol, P.H. Ithin, Diagnosis and treatment of lichen sclerosus. An update, Am. J. Clin. Dermatol. 14 (2013) 27–47.