

Two cases of disseminated superficial actinic porokeratosis (DSAP) and treatment literature review

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ABSTRACT

Background: Disseminated superficial actinic porokeratosis (DSAP) is characterized by asymptomatic multiple papules with annular keratotic rim distributed symmetrically on the sun-exposed areas. Many approaches have been proposed in the past for treating DSAP, but the therapy is still a challenge for every physician, mostly because of the frequent relapses of the disease and the multiplicity of the skin lesions. **Material and Methods:** Two case reports were reported emphasizing the challenges of treatment approach. Therefore, a systemic English literature review was conducted searching Medline database using PubMed Central and Ovid software as search interface to collect evidence based on the various treatment modalities for DSAP. **Results:** The initial search yielded 146 articles, but only the relevant case reports, case series and studies relating to the treatment of DSAP have been described and summarized in a table. For each different therapy the efficacy of each treatment, side effects, cost-effectiveness and authors' recommendations were reported. **Conclusion:** Several factors need to be considered prior to physicians' decision of the most appropriate treatment for each patient like age, the extent of body surface area involvement, patients' medical history and social situation, the available resources, the side effects and cost-effectiveness of each treatment. However, the exact value of each treatment is difficult to determine owing to the lack of controlled studies evaluating their efficacy. Due to few incidences of squamous cell carcinoma, patients need to be followed up and monitored closely for any early detection of recurrence or possible onset of malignancies.

Key words: Porokeratosis; Keratinizing disorders; Lasers; Photodynamic therapy

INTRODUCTION

Disseminated superficial actinic porokeratosis (DSAP) was first described by Chernosky and Freeman [1]. Clinically, DSAP is characterized by asymptomatic multiple papules with annular keratotic rim distributed symmetrically on the sun-exposed areas, and facial involvement is a rare presentation¹. Malignant degeneration has been described in 7% to 11% of porokeratoses cases, with squamous cell carcinoma being the most common [2-4]. Histological hallmark is the cornoid lamella, which is formed by clonal hyperproliferation of atypical keratinocytes [3]. Underlying the cornoid lamella, the granular layer is thinned or absent and keratinocytes are oedematous with spongiosis, and dermal lymphocytic infiltrate

may also be evident [5]. Dermoscopy examination demonstrate single or double "white track" structure at the margin corresponding to the cornoid lamella, and the red dots, globules, and lines are enlarged capillary vessels that can be observed because the epithelium is atrophic [6].

Xia and colleagues using a genomewide search in a large Chinese family, identified a locus at chromosome 12q23.2-24.1 responsible for disseminated superficial actinic porokeratosis [7]. Therefore, DSAP is an inherited dermatologic disorder with lesions appearing in genetically predisposed individuals after adequate exposure to ultraviolet radiation or immunosuppression in the third and fourth decades of life [8].

How to cite this article: Thomaidou E, Katz M, Leibovici V. Two cases of disseminated superficial actinic porokeratosis (DSAP) and treatment literature review. Our Dermatol Online. 2018;9(3):241-248.

Submission: 16.10.2017; **Acceptance:** 13.01.2018

DOI:10.7241/ourd.20183.3

A variety of approaches have been proposed to treat DSAP, but the therapy is still a challenge for every physician, mostly because of the multiplicity of the skin lesions and the frequent relapses of the disease [9]. Herein, we present two case reports with a great dilemma in treatment approach, following by an update literature review.

CASES

Case 1: An eighteen four-year-old man presented in our clinic with 6-month history of bilateral symmetrical erythematous skin lesions on the lower and upper extremities. The skin eruptions were associated with photosensitivity and moderate pruritus. The patient had a background medical history of hypercholesteremia, hypertension, ischemic heart disease, congestive heart disease, diabetes mellitus type 2, non-alcoholic fatty liver, chronic renal failure and glaucoma.

On examination bilateral erythematous scaly papules with annular configuration, well-demarcated borders and central atrophy were seen on the shins, thighs and forearm (Figs. 1a and 1b). Dermoscopy examination revealed a white like track structures at the periphery of the lesion with a mild hyperpigmentation in the inner side and with some red globules, and lines at the periphery (Fig. 2). On histological examination cornoid lamella was found in the stratum corneum with focal loss of granular layer, prominent lichenoid, superficial perivascular lymphocytic infiltrate and background elastosis (Figs. 3a and 3b).

Case 2: An eighteen one-year-old man with background history of diabetes mellitus type 2, bronchiectasis, asthma, ischemic heart disease, aortic stenosis and mitral insufficiency was examined in our clinic due to 3-year history of annular non-pruritic lesions on the shins. In the past, he was treated with steroid intralesional injections without any improvement.

On examination, there were multiple annular erythematous lesions with central clearing and elevated borders on the shins (Figs. 1c and 1d). Histological examination revealed cornoid lamella with absence of the granular layer. The intervening epidermis between the cornoid lamellae was thin and in the upper dermis there were perivascular mononuclear and lichenoid cells.

According to the clinical and histological presentation, both of our patients were diagnosed with disseminated superficial actinic porokeratosis. Their clinical presentation, risk of malignancy, medical history and

their social situation was considered for choosing the most appropriate treatment for the patient.

Prior to the study, patient gave written consent to the examination and biopsy after having been informed about the procedure.

METHOD

A systemic English literature review was conducted in June 2017 searching Medline database using PubMed Central and Ovid software as search interface to collect



Figure 1: (a-d) Bilateral erythematous scaly papules with annular configuration on the shins, thighs and forearm with well-demarcated borders and central atrophy.



Figure 2: A "white track" structures can be identified at the periphery of the lesion with a brownish pigmentation in the inner side and with some red globules, and lines at the periphery.

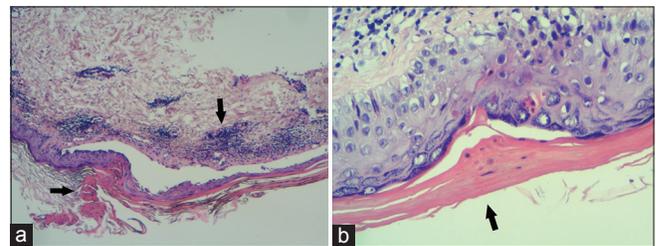


Figure 3: (a and b) Cornoid lamella was found in the stratum corneum with focal loss of granular layer, prominent lichenoid, superficial perivascular lymphocytic infiltrate and background elastosis. (Hematoxylin and Eosin, 40x, 400x).

Table 1: Review of treatments modalities. DSAP - Disseminated Superficial Actinic Porokeratosis; N/A – Non-Applicable. ;MAL-PDT - Methyl-aminolevulinatate Photodynamic Therapy. ; ALA-PDT- Aminolaevulinic acid Photodynamic Therapy; Nd: YAG - neodymium-doped yttrium aluminium garnet

Author	Type of study	Therapy	Number of patients	Age of patients	Mechanism of action	Efficacy	Side effects	Cost	Authors' recommendations
Topical treatment Vlachou <i>et al.</i> , 2008 10	Case series	Topical Diclofenac 3%	8	51-79	Diclofenac exerts its action via inhibition of prostaglandin synthesis by inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), causing inhibition of arachidonic acid metabolism, thereby reduction of the tumorigenic effects of its metabolites	Completion of the therapy: 6/8 patients had no improvement and 2 had partial improvement	Pruritus Erythema	Inexpensive	A non-invasive, generally well tolerated and relatively safe topical therapy, but the results do not support its effectiveness on DSAP The data implies that the treatment provided some protection against disease progression, and it would be helpful in the absence of desirable alternatives
Marks <i>et al.</i> , 2009 11	Open-label, multicenter pilot study		17	N/A		12 th weeks: 7/13 patients had a decrease in number of lesions, and 1 patient had a stable number of lesions on the target area Completion of the therapy (24 th week): 3/10 patients had a decrease in number of lesions, and 1 patient had a stable number of lesions	Dermatitis Erythema		
Otero-Rivas <i>et al.</i> , 2016 12	Letter to the Editor		1	82		Completion of the therapy (12 th week): almost all lesions had cleared and only some erythematous macules persisted	No side effects		It is a well-tolerated and safe topical therapy with excellent results in the treatment of DSAP and it could be useful in some selected patients
Arun, Pearson, Chalmers 2011 13	Case report	Imiquimod 5% cream	1	68	Toll-like receptor (TLR) agonist, stimulating the innate immune response by activating antigen-presenting cells to produce interferon and other cytokines and chemokines. It may suppress or switch off the abnormal mutant genes through its immunological effects	Completion of the therapy (8 th week): slight superficial scarring and residual erythema, but no evidence of the original condition	Superficial scarring Residual Erythema	Inexpensive	It may be a useful treatment option, but it should be introduced cautiously, and an application frequency of three times a week should be used initially to avoid excessive inflammation
Riad <i>et al.</i> 2013 14	Case report		1	19		Completion of the therapy: only few lesions with a partial response and no relapse after 2 years	Erythema, Pruritus		N/A
Harrison, Stollery 1994 15	Letter to the Editor	Calcipotriol	3	68-85	Vitamin D3 analogs may induce genes critical for keratinocyte differentiation, such as transglutaminase or involucrin; and may inhibit proliferation by inducing sphingomyelin hydrolysis and modulation of protein kinase C activity	Completion of the therapy: improvement varied between 50 and 75%, which was maintained for up to 6 months in 2/3 patients	Skin irritation	Inexpensive	N/A
Bakardzhiev, Kavaklieva, Pehlivanov, 2012 16	Letter to the Editor	Calcipotriol	1	73		Completion of the therapy: after 6-month patient was free of lesions	Non-reported	Inexpensive	Good response of DSAP to calcipotriol has documented.

Contd...

Table 1: (Continued)

Author	Type of study	Therapy	Number of patients	Age of patients	Mechanism of action	Efficacy	Side effects	Cost	Authors' recommendations
Böhm, Luger, Bonsmann, 1999 17	Case report	Tacalcitol	1	40		Completion of the therapy: 5-month lesions had completely faded and only few invisible lesions were noticeable on palpation	Non-reported		Vitamin D3 analogs may help to reduce the long-term risk of malignant transformation.
Nakamura <i>et al.</i> , 2014 18	Case report	Calcipotriol and adapalene	1	63		Completion of the therapy: after 3 months skin lesions improved substantially	Hyperpigmentation		The lack of significant adverse effects and clinical efficacy, indicates that the treatment may represent a useful option
Tchernev <i>et al.</i> , 2017 19	Case report	Calcipotriol/ betamethasone gel	1	80		Completion of the therapy: after 2 months almost full resolution of the clinical symptoms and without the appearance of fresh lesions	No side effect		The lack of significant adverse effects in the patient, as well as the good tolerance and the significant clinical improvement, indicates that this treatment option is beneficial for the therapy of DSAP
Systemic Therapy									
Kariniemi, Stubb, Lassus, 1980 20	Case report	Aromatic retinoid	1	84	Vitamin A derivatives may participate in the differentiation of the epidermal cells and enhance keratinization, leading to reduction of the mitotic activity	Completion of the therapy: after the 40 th day, the pruritus had stopped entirely, and the lesions had cleared so that the scaly thread-like border had disappeared	Mild cheilitis Hair loss	Inexpensive	N/A
Ludera-Zimoch, Rubisz-Brzezinska, 1989 21	Case report		1	55		Completion of the therapy: after the 3 rd month, clinical improvement lasted for several months and their followed by less pronounced but progressive reappearance of clinical symptoms	N/A		N/A
Carmichael, Tan, 1990 22	Case report	Etretinate	1	55		Completion of the therapy: after the 2 nd month marked improvement in the scaling, but treatment stopped due to side effects	Hair thinning Digitate keratoses		N/A
Photodynamic Therapy (PDT)									
Cavicchini, Tourlaki, 2006 9	Letter to the Editor	MAL-PDT	1	50	Topical methyl aminolevulinat (MAL), photosensitizing drug with appropriate light dose can result to highly reactive oxygen species leading to selective cell damage and indirectly stimulate inflammatory cell mediators	Completion of the therapy: after the 12 th month, no new lesions occurred, and a striking clinical improvement was observed with only a slight residual hyperpigmentation	Burning sensation Hyperpigmentation	Expensive	MAL-PDT showed high efficacy and good cosmetic outcome with a high patient satisfaction level

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Table 1: (Continued)

Author	Type of study	Therapy	Number of patients	Age of patients	Mechanism of action	Efficacy	Side effects	Cost	Authors' recommendations
Fernandez-Guarino et al., 2009 23	Letter to the Editor	MAL -PDT	6	55-74		Completion of the therapy: after 2 weeks: 2/6 showed no respond, 4/6 showed slight reduce roughness	No side effects were noted	Expensive	DSAP with MAL-PDT suggest that this treatment may not be promising for this dermatosis
Salas et al., 2016 2	Case report		2	58,73		Completion of the therapy: after 10 months good results remained and no evidence of recurrence in the treated lesions	No side effects were noted		Two cases of DSAP treated successfully with daylight-PDT with no recurrence after 10 months
Nayeemuddin et al., 2002 24	Case series	ALA-PDT	3	42-59	5-aminolaevulinic acid (5-ALA) is a pro-drug, which relatively selectively is taken up by some skin diseases and it has the same mechanism of action with MAL when combine with appropriate light dose	Completion of the therapy: After the second treatment 3/3 patients decided not to continue the treatment because 2/3 did not respond, 1/3 had post -inflammatory hyperpigmentation	Discomfort, Skin peeling Pigmentary changes	Expensive	The results of ALA-PDT in these three patients suggests that this treatment modality may not be suitable for DSAP
Boiy , de Witte, Roelandts 2010 25	Case report	Hypericin-PDT	1	54	Hypericin is a photo-active dye originating from the herb Hypericum perforatum (St. John's wort)	Completion of the therapy: After three treatments, little or no clinical improvement was noted	Erythema	Expensive	Topical hypericin-PDT does not emerge as a promising treatment for DSAP
Lasers and Lights Lolis , & Marmur, 2008 3	Case report	Q-switched ruby laser (694nm)	1	48	N/A	Completion of treatment: most of the lesions decrease	Erythema Hyperpigmentation	Expensive	Ruby laser (694 nm) has a great degree of penetration, allowing it to treat pigmented lesions which occur deeper in the dermis affecting mainly post -inflammatory hyperpigmentation of the lesion
Itoh, & Nakagawa, 2007 26	Case report	Q-switched Nd: YAG laser (532nm)	1	61	N/A	Completion of treatment: most of the lesions improved with no residual skin lesions	Hyperpigmentation		The Q-switched ruby laser (QSRL) may be useful for the treatment of DSAP
Lui , 2010 27	Case report	Q-switched Nd: YAG laser (532nm)	1	56	N/A	Completion of treatment: good improvement of most of the lesions with patient satisfaction and unchanged results after 9 months follow up	N/A		N/A
Rosenblum, 2013 28	Case report	Erbium and neodymium YAG lasers	1	62	N/A	Completion of treatment: good improvement of the majority of the lesions	Erythema		N/A

Contd...

Table 1: (Continued)

Author	Type of study	Therapy	Number of patients	Age of patients	Mechanism of action	Efficacy	Side effects	Cost	Authors' recommendations
Ross <i>et al.</i> , 2016 29	Case report	Fractional 1927nm thulium fiber lasers	2	46,65	N/A	Completion of treatment: No new lesions, decrease the thickness of remaining lesions	Edema Erythema	Expensive	It is convenient and safe with nearly no downtime or morbidity associated with pigment or textural defects. Conducting multiple treatments versus one and more aggressive treatment are needed due to the poor wound healing properties on the lower extremities N/A
Chrasil <i>et al.</i> , 2007 30	Case report	Fractional Photo-thermolysis	2	47,48	The stimulatory effects of fractional resurfacing on dermal collagen remodeling and epidermal regeneration, in addition to the reversal effects on photodamaged skin, are mechanisms that might explain the successful treatment of DSAP	Completion of treatment: greater than 50% improvement of the lesions was noted and full patient satisfaction	Erythema		
Noborio , Morita, 2011 31	Letter to the Editor	CO2	1	83	N/A	Completion of treatment: majority of lesions disappear, satisfy patient and no recurrence on the follow up	N/A		CO2 laser therapy is mostly effective, but severe scarring is an occasional adverse effects of conventional CO2 laser irradiation
Kim <i>et al.</i> , 2011 32	Case report	CO2+PDT	2	61,62	N/A	Completion of treatment: majority of lesions disappear with no recurrence on the follow up	Hyperpigmentation Aggravation of melasma		Overall, PDT was found to remove some of the remnant rims of DSAP following CO2 laser ablation, but the degree of improvement was not striking. Using MAL-PDT to CO2 laser vaporization, multiple sessions of treatment are required, and complications associated with PDT raised some concern
Ricci, Rosset, Panizzon, 1999 33	Case report	Grenz rays	1	77	X-rays are known to have antiproliferative activity by inhibition of the DNA synthesis, particularly in abnormal cells, apart from their potent anti-inflammatory effect	Completion of treatment: after two years they were excellent outcomes, no recurrence	Pruritus	Expensive	It may be a useful option in the management of elderly patients with DSAP

evidence based on the various treatment modalities for DSAP. In addition, studies that have been commonly cited in the literature and review articles were included as citation search engine to identify subsequent publications, which were relevant for the literature review. The following medical terms and text world were used: “Disseminated superficial actinic porokeratosis”, “porokeratosis”, “laser”, “photodynamic therapy”, “diclofenac”, “calcipotriol”, “imiquimod”, “retinoid”, “photodynamic therapy”, “lasers”. The keywords were combined using multiple combinations. Articles that did not mention treatment approaches, which were not published in English or were not available, have not been included for the purposes of this literature review. Any discrepancies about data evaluation of the selected articles were resolved after discussion between the authors.

RESULTS

The initial search yielded 146 articles, but only the relevant case reports, case series and studies relating to the treatment of DSAP have been described below and summarized in Table 1. For each different therapy the efficacy of each treatment, side effects, cost effectiveness and authors’ recommendations were reported.

DISCUSSION

Traditional topical treatment approaches include topical treatments like diclofenac [10-12], imiquimod [13-14] and calcipotriol [15-19]. Oral retinoids [20-22] and cryotherapy [15] were used in the past with no any satisfied results. Newer treatment of photodynamic therapy (PDT) [2,9,23-25] and lasers [3,26-32] have been introduced in the recent years with some desirables results. A literature review was conducted five years ago assessing the level of evidence for some therapeutic modalities. However, still the exact value of each treatment is difficult to determine owing to the lack of controlled studies evaluating their efficacy [5].

Several factors need to be considered for choosing the most appropriate treatment for each patient, like the age, the extent of body surface area involvement, patients’ medical history and their social situation, the available resources in dermatology departments, the side effects and cost effectiveness of each treatment approaches. Systemic treatment might not be an option if patients have complicated medical background and

take multiple medications, due to possible interactions of retinoids with their regular medications. Expensive treatment like different types of lasers can be discussed with the patients but usually are not considered due to the high cost and lack of experienced centres. PDT therapy showed poor outcome in several studies (e.g. six out of nine patients had none or minimal response with MAL- PDT, all patients had no response with ALA-PDT and Hypericin-PDT), thus it is not recommended frequently [2,9,23-35].

Following a thorough discussion among physicians in our clinic, both patients started on topical treatment with calcipotriol/betamethasone gel with partial resolution. Patients are under follow up and they will be monitored closely for any possible onset of malignancies. In conclusion, there are several options available for treating DSAP, but always the best approach should be tailored to every patient. There is still a great need for further controlled studies with a greater sample size to draw conclusions on the effects of these novel treatments for DSAP.

Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

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Source of Support: Nil, Conflict of Interest: None declared.