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Original Research—Case Report

Combination of Laser Therapy and Photodynamic Therapy with 5-Aminolevulinic Acid Patch for the Treatment of Actinic Cheilitis

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Abstract

Background: Actinic cheilitis (AC) is a premalignant lesion of the lips that can evolve into squamous cell carcinoma. Among nonsurgical treatments, photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA) patch might represent a new noninvasive therapeutic approach for AC.
Objective: We sought to investigate the potential role of fractional CO_2 laser pretreatment in boosting ALA penetration and distribution into AC treated with PDT.
Methods: We report a case of a woman with AC on the lower lip, treated with ablative fractional CO_2 laser to boost drug delivery of 5-ALA patch before PDT treatment. Reflectance confocal microscopy was performed to assess diagnosis and treatment response.
Results: We detected a good clinical and cosmetic outcome after two applications of combined treatment. Erythema, crust, and edema were reported as side effects.
Conclusions: This case report shows that ablative fractional CO_2 laser-assisted PDT might be an effective therapeutic alternative for patients with AC who refuse or are contraindicated for surgical procedures.

Keywords: actinic cheilitis, fractional CO_2 laser, ALA patch PDT, photodynamic therapy, drug delivery

Introduction

ACTINIC CHEILITIS (AC) is considered to be the counterpart of actinic keratosis (AK) and frequently affects the vermilion border of the lower lip. The anatomical position and the prominent shape of the lips make them more susceptible to UV radiation, irritants, trauma, and viral infections.[1] Moreover, the skin type of the vermillion is described as a transition between buccal mucosa and normal skin and has a thinner epithelium that lacks keratin covering, with less melanin and reduced secretions from the sebaceous and sweat glands. All these features contribute to the increased susceptibility to solar radiation.[2]

Similarly to AK of the skin, AC is considered to be a possible malignant oral lesion or even a lip *in situ* squamous cell carcinoma (SCC).[3,4] The clinical presentation of AC is characterized by a gray-whitish scaly plaque with a rough texture on palpation. Nevertheless other clinical presentations, such as erosions, ulcerations, and vermilion border atrophy, might also occur.[5]

The global prevalence of AC is estimated to be between 0.45% and 2.4% and increases up to 43.2% in patients with risk factors.[6] Further, an estimated 95% of SCCs of the lip arise from AC.[7]

Reflectance confocal microscopy (RCM) is a noninvasive imaging procedure with near cellular resolution that allows for the diagnosis of AC *in vivo*. Typical findings in ACs are characterized by single detached corneocytes and parakeratosis, represented by nucleated cells in the stratum corneum; atypical honeycomb pattern in the stratum granulosum and spinosum is characterized by variation in cell size and morphology.[8] The differential diagnosis involves inflammatory disorders of the lips, such as benign leukoplakia, lichen planus, lip eczema, cheilitis granulomatosa, or simply dry skin and chronic irritation.[9]

Various therapeutic approaches are available for the treatment of AC, which can be nonsurgical or surgical.[10] Surgical treatments (vermillectomy) consist of the destruction of involved tissue with cryosurgery, scalpel, electrosurgery, or laser ablation. Nonsurgical therapies include imiquimod, diclofenac,

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5-fluorouracil, ingenol mebutate, and trichloroacetic acid that are recommended for the treatment of AC.[11,12] Photodynamic therapy (PDT) is another available therapeutic approach.[13] In conventional PDT, a photosensitizer, usually aminolevulinic acid (ALA) or methyl-ALA, is topically applied and covered with an occlusive dressing for ~2–3 h. After the photosensitizer has been absorbed into the dysplastic and neoplastic cells, it is metabolized and activated into protoporphyrin IX (PpIX). Illumination in the appropriate light spectrum causes formation of and subsequent photochemical destruction of the pathological tissue.[14] Several reports have shown that PDT can be considered a successful and safe nonsurgical approach for the management of AC.[15]

Recently a 5-ALA patch (Alacare, photonamic GmbH and Co. KG, Pinneberg, Germany) has been introduced for the treatment of AKs with PDT. The patch is 2×2 cm, contains 2 mg of ALA per cm^2, and requires 4 h of incubation per lesion. This is a simple application approach because it does not require additional occlusive dressing.[16] A recent study on 21 patients has demonstrated promising results in the treatment of ACs with Alacare, with complete remission in 84.2% at 12-month follow-up.[17]

The response to nonsurgical therapy is often unsatisfactory, due to the high recurrence rate observed after treatments. Also, several studies showed that topical therapies including PDT are less efficient in the treatment of ACs compared with AKs.[12] This observation was recently confirmed by two comparative studies proving that classic PDT is not as effective for ACs as it is for AKs.[15,18] A limitation to treatment response can be related to an inadequate photosensitizer absorption in the deeper skin layers.[19] Recently, *in vivo* and *in vitro* experimental studies showed that pretreatment of the skin with ablative fractional lasers improves the absorption of photosensitizers and enables intracutaneous distribution into deeper skin layers.[20–23]

Drug delivery with ablative fractional CO_2 laser may improve the performance of PDT by increasing the bioavailability of the photosensitizer within deeper skin layers, reducing the incubation time, and enhancing the PDT response.[24]

Case Report

We report a case of a 72-year-old Caucasian woman, Fitzpatrick skin type II, who presented to our department with several erythematous scaly patches on her nose and ears, diagnosed as AKs. Closer examination of her lower lip revealed linear fissures, erosions, and an altered vermilion border, which was clinically compatible with the diagnosis of AC, which has never been treated before (Fig. 1). Dermoscopically, the lip was characterized by white structureless areas and scale (Fig. 2). The diagnosis of AC was also confirmed by RCM (Vivascope® 1500; Lucid-Tech, Inc., Henrietta, NY, USA; Mavig GmbH Munich, Germany), which revealed an atypical honeycomb pattern with irregular cell shape and size and parakeratosis (Fig. 3).

With the patient's informed consent and ethical committee approval, we treated her with ablative fractional CO_2 laser in combination with the conventional 5-ALA patch PDT. We performed two sessions spaced 40 days apart. Before each session, a 7-day course of acyclovir 800 mg was administered twice a day to prevent herpes viral infections. The area was prepared with topical anesthesia with 5% prilocain–lidocain cream 1 h before the treatment.

FIG. 1. Clinical aspect of actinic cheilitis characterized by a grayish-whitish scaly plaque with a sandpapery texture on palpation.

After anesthetic cream removal and skin disinfection, a laser session with SmartXide2® ablative fractional CO_2 laser (DEKA-M.E.L.A, Calenzano, Italy) was performed. Laser parameters were wavelength 10.600 nm, power 20 W, pulse width 100 μs, repetition rate 500 Hz, spot density 15×15 mm (328 spots/cm^2), and beam size of 200 μm, resulting in a mild dermoabrasion of the lower lip. Immediately afterward, three 5-ALA patches (2×2 cm) were applied on the AC area of the lower lip without requiring additional occlusive dressing. After a 2-h incubation, the patches were removed and the Wood's lamp revealed an intensive and homogeneous fluorescence of the lower lip. The treated area was then irradiated with red light-emitting diode lamp (Aktilite® 128 lamp; Galderma SA, Lausanne) with the peak emission at 632 nm and total light dose of 37 J/cm^2 for 7 min.

At the end of the session, the patient exhibited erythema and swelling of the lower lip. Throughout the procedure, the patient assessed the perception of pain as moderate (5710), according to the Pain Visual Analogue Scale (PAIN VAS) scale from 0 to 10, considering the effect of local anesthesia. The recovery period, however, was complicated by

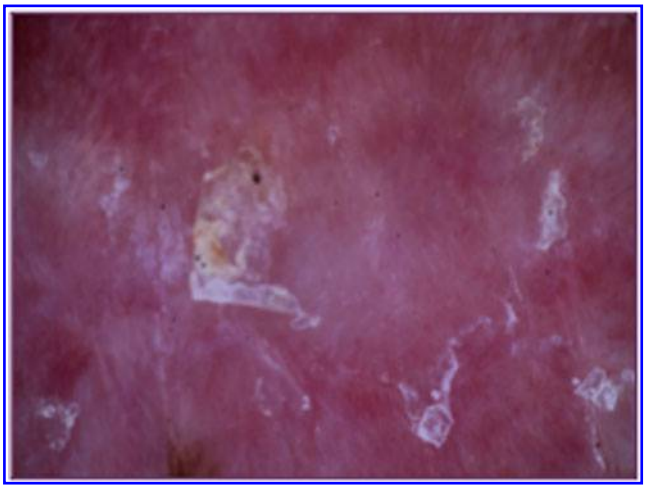

FIG. 2. Dermoscopic aspects of actinic cheilitis at baseline characterized by white structureless areas and scales.

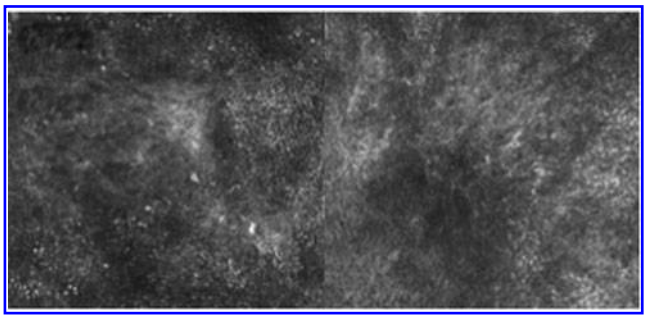

FIG. 3. RCM of actinic cheilitis revealed atypical honeycomb pattern with irregular cells size and shape, scales, and parakeratosis. RCM, reflectance confocal microscopy.

FIG. 5. Clinical appearance at 6-month follow-up.

moderate swelling, erythema, and crust formation for up to 2 weeks (Fig. 4) with moderate limitations of functional oral activities for 14 days as reported by the patient. These adverse events were managed with greasy dressings of hyaluronic acid and topical antibiotics for 7 days. The patient completed a second procedure 2 months after her first session. Complete clinical remission with an excellent cosmetic outcome, as well as no relapses, was observed at the 6- and 12-month follow-up visits (Figs. 5 and 6). The clinical results were also confirmed through RCM at each follow-up visit, which revealed complete recovery of the labial mucosa with honeycomb appearance of the epidermis (Fig. 7).

Discussion

AC is a common precancerous lesion, which mostly affects the inferior lips. Risk factors of AC include advanced age, fair skin photo type, and cumulative UV exposure. Given its propensity to progress into SCC, AC needs to be promptly treated.

Currently there is no general consensus on the treatment of AC. Surgery is often a largely demolitive procedure not well tolerated by patients. In contrast, noninvasive treatments showed a lower rate of complete clinical success. PDT represents a valid noninvasive treatment option although it showed relatively low levels of complete response in AC.[12]

Recently a new medical device 5-ALA patch has been experimented for the treatment of AC with PDT.[17] Fixation on the lips is quick and simple, avoiding the occlusive dressing that is otherwise difficult to apply on the lip; moreover, dilution of the applied ALA by saliva is completely prevented by the patch formulation. ALA patch treatments have a relatively long downtime, as 4 h incubation time is necessary. Moreover, due to the intrinsic characteristic of AC, ALA may be less effective for the treatment of AC compared with AK. The long incubation time and the uncertain outcome make the procedure difficult for both physicians and patients.

To overcome these obstacles, we decided to combine CO_2 fractional ablative laser with 5-ALA patch PDT to reduce incubation times and facilitate the absorption of the photosensitizer. The therapeutic efficacy of photosensitizers, indeed, is related to their percutaneous absorption and their ability to reach target cells.[20] Bay et al. demonstrated how combination of PDT with laser pretreatment improved PDT efficacy by enhancing the absorption of the photosensitizer.[24] In relation to this, ablative fractional CO_2 laser is an attractive therapeutic approach that reduces outer skin layers and generates microscopic vertical channels of microablated tissue, each surrounded by a thin layer of coagulated tissue, representing microscopic treatment zones.[21] These combined effects could explain the enhancement of drug uptake and acceleration of intracutaneous biodistribution.

In support of this observation, the Wood lamp examination clearly revealed an intense bright red fluorescence of the lower lip after patch removal, indicating high accumulation of PpIX. In our experience, this combination approach could be useful to reduce the approved 4-h incubation time of the 5-ALA patch, as we reached an excellent clinical result even with 2-h incubation, which is clearly advantageous for both patients and physicians. No clinical recurrence at 6- and 12-month follow-up was observed; this result has been confirmed with RCM showing recovery of the

FIG. 4. Clinical appearance after 2 weeks of treatment. Side effects of the treatments include swelling erythema and crusts.

FIG. 6. Complete clearance at 12-month follow-up.

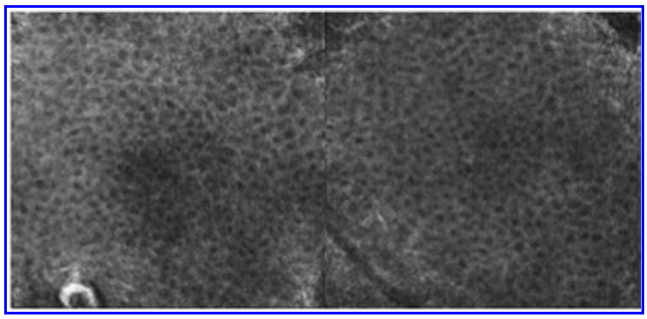

FIG. 7. RCM revealed complete recovery of the labial mucosa with honeycomb appearance of the epidermis at 12-month follow-up.

honeycomb pattern. Moreover, the utilization of topical anesthesia significantly reduced the pain associated with the procedure. Side effects, such as swelling, erythema, and crust, were easily managed and resolved in 2 weeks without scarring. Nevertheless, this is a traumatic treatment, during which the integrity of the mucosa and skin is altered, increasing susceptibility to both viral and bacterial infections. For this reason, antibiotic and antiviral prophylaxis was prescribed. Thus, this promising result warrants further larger investigations to adequately assess the long-term efficacy, the optimal assessment, and duration of the treatment in wider populations.

Conclusions

Owing to the high chance of AC to evolve to SCC, effective treatments with satisfactory cosmetic outcomes are needed. Combining the low complexity of nonsurgical techniques with the efficacy of surgical procedures, fractional CO_2 laser-assisted PDT provides a promising alternative for AC. The method overcomes the detrimental effects of surgery and the inferior efficacy of conservative nonsurgical techniques. In conclusion, 5-ALA patch delivery with CO_2 fractional ablative laser is easily performed, reduces downtimes in PDT, and represents a promising noninvasive therapeutic approach for the treatment of AC.

Table 1. Table of Laser Parameter

Manufacturer	*Deka*
Model identifier	SmartXide2®
Year produced	2011
Number and type of emitters (laser or LED)	One laser
Wavelength and bandwidth (nm)	10.600
Pulse mode (CW or Hz, duty cycle)	Pulsed 500 Hz
Beam spot size at target (cm^2)	200 μm
Irradiance at target (mW/cm^2)	—
If pulsed peak irradiance (mW/cm^2)	10^9
Exposure duration (μs)	100
Radiant exposure (J/cm^2)	127
Radiant energy (J)	0.04
Number of points irradiated	328
Area irradiated (cm^2)	2.25
Application technique	Fractional
Number and frequency of treatment sessions	Two every 40 days
Total radiant energy over entire treatment course (J)	9.5

PBM, photobiomodulation.

Author Disclosure Statement

No competing financial interests exist.

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