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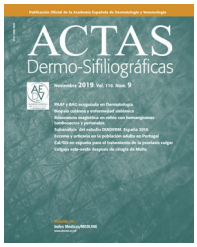

CASE AND RESEARCH LETTER

Refractory Lichen Sclerosus Treated With Fractional CO_2 Laser-assisted Drug Delivery Photodynamic Therapy Using 5-Aminolevulinic Acid: A Case Series

Liquen escleroso refractario tratado con terapia fotodinámica con ácido 5-aminolevulínico asistido por láser de CO_2 fraccionado: serie de casos

To the Editor,

Lichen sclerosus (LS) is a chronic inflammatory mucocutaneous disease[1] that has a huge impact on the patients' quality of life.[2] Ultrapotent topical corticosteroids (UPTC) do not always control symptoms and have been associated with deleterious local adverse effects,[3] which exacerbates LS symptoms. Other non-invasive approaches such as photodynamic therapy (PDT) or laser therapy yield promising results.[3,4] However, as far as we know, the combination of the two has never been reported to this date.

We conducted a descriptive retrospective analysis on patients on combined therapy with fractional microablative CO_2 laser (FMCL) and PDT for refractory LS in two different dermatology departments. Therapy was administered as an outpatient procedure under topical anesthesia, although this modality could modify further drug absorption. Initially, we performed FMCL over the treatment area using two CO_2 laser devices depending on the availability of each center (Table 1), followed by the administration of 1 g of 5-aminolevulinic acid 78 mg/g (Ameluz®, Biofrontera, Leverkusen, Germany) for every 25 cm^2 of affected skin placed under occlusion for 90 min. Afterwards, the patient was positioned to expose the maximum affected area (e.g. with legs abducted and flexed to expose the genital area) which was then exposed to the PDT lamp BF-RhdoLED® (Biofrontera) for 20 min (wavelength 630 nm, light dose 37 J cm^{-2}). If necessary, treatment was readministered after a 6-week interval. Disease activity was assessed using the Investigator's Global Assessment (IGA, 0–3), and the LS-related pain was rated using a visual analogue scale (VAS, 0–10). Patients were also asked about their pain during sexual activity. These assessments were conducted before and 3 months after therapy. Patient satisfaction with the procedure was rated from 0 to 100. Pre- and post-treatment results were compared using the paired-sample Wilcoxon test. This study was approved the Ethical Board, and all patients signed the corresponding written informed consent form.

We included five women. Table 1 illustrates main characteristics of patients and lesions treated. A significant reduction in the IGA score was observed between baseline (3 [2–3]) and after treatment (0 [0–2]) ($p = 0.01$). The median pre-treatment VAS score was 10 (8–10) and the post-treatment VAS score, 3 (0–4), which was significantly lower ($p = 0.041$). The median satisfaction level with the procedure was 90 (80–100). Treatment was well tolerated, and no severe adverse events were reported. Mild and transient erythema, edema and crusting were reported in all the patients. Two patients were sexually active before treatment, experiencing pain with intercourse. They were able to resume painless sexual activity after treatment. No relapses or presence of squamous cell carcinoma were reported in the area at the 36.4-month follow-up (7.2–40.5). Fig. 1 illustrates the results in 1 patient after 1 session of treatment.

PDT targets inflammatory cells, generating intracellular reactive oxygen species through the interaction of a photosensitizing agent, directed at these cells, and an appropriate light wavelength for agent activation.[1] PDT prompts apoptosis in the target tissue, without damaging the surrounding healthy skin.[5] PDT has been associated with alleviation of subjective LS symptoms such as pruritus and pain, along with an improvement in patients' quality of life.[5]

On the other hand, FMCL induces a superficial ablative effect on the tissue while stimulating the production of collagen and elastic fibers. This process helps restore epithelial trophism and remodel the connective tissue of the dermis.[3,4] Recent findings indicate that FMCL provides clinical benefits to as many as 89% of LS patients, a significantly higher proportion vs those using topical corticosteroids.[6]

The use of a fractionated ablative laser to increase the uptake of topical treatments, termed laser-assisted drug delivery, has already been explored in several skin diseases.[7,8] The combination of fractional CO_2 laser with PDT has demonstrated greater effectiveness vs PDT alone in conditions such as actinic keratosis[9] or basal cell carcinoma.[10] Our findings suggest that combining these two techniques could yield synergistic effects also in LS patients arising not only from the distinct skin structures targeted by each

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Table 1 Summary of the patients' characteristics and outcomes and lasers used.

Patient	Age	Ancestry and phototype	Location of lesions	IGA			Pain VAS			Satisfaction with the procedure	No. of sessions	CO_2 laser	FMCL parameters
				Pre-treatment	Post-treatment	*p*	Pre-treatment	Post-treatment	*p*				
1	73	Caucasian, 3	Inframammary left	3	0	0.01	10	0	0.041	100	2	UltraPulse® Encore™ by Lumenis	Energy: 150 mJ Density: 3/9 Stack: 1
			Inframammary right	3	0						2		
			Back	2	0						1		
2	64	Caucasian, 2	Genitalia	3	2		8	4		90	1	UltraPulse® Encore™ by Lumenis	Energy: 150 mJ Density: 3/9 Stack: 1
3	45	Caucasian, 2	Genitalia	2	0		10	0		100	1	Fraxis by Creative Ilooda®	Energy: 32 mJ Distance: 0.7 mm Stack: 1
4	52	Caucasian, 3	Genitalia	3	1		10	3		90	2	Fraxis by Creative Ilooda®	Energy: 30–42 mJ Distance: 0.7 mm Stack: 1
5	49	Caucasian, 3	Genitalia	3	1		10	3		80	1	Fraxis by Creative Ilooda®	Energy: 32 mJ Distance: 0.7 mm Stack: 1
			Inframammary	3	0						1		

Abbreviations: Fractional microablative CO_2 laser (FMCL) type and parameters applied; IGA: Investigator's Global Assessment; VAS: visual analogue scale.

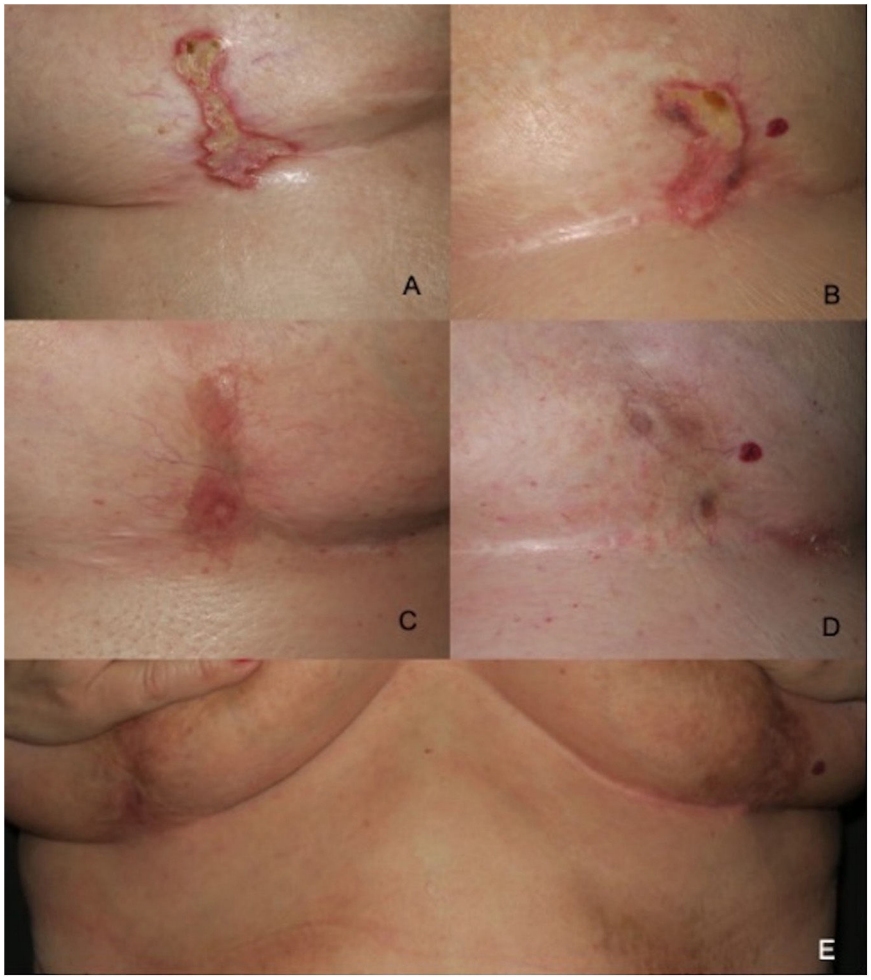

Figure 1 Inframammary lichen sclerosus lesions in patient no. 1 before treatment (A, right; B, left), before 2nd laser session (C, right; D, left) and at the 1-year follow-up (E).

technique but also due to FMCL potential to enhance drug permeation, thereby amplifying the effects of PDT.[7]

There may be concerns on the tolerability of this approach due to pain reported during PDT.[5] In our experience, conducted under topical anesthesia, the combination of FMCL plus PDT is a safe and well tolerated procedure.

The main limitations of our study are its retrospective design, the limited number of patients, and the use of two different laser devices. However, we adjusted the settings to create similar laser microchannels.

This is the first case series ever reported to describe the combination of FMCL + PDT to treat refractory LS. This treatment approach seems to be effective in terms of improving disease activity and pain relief, including pain during intercourse, with no associated adverse events, representing a promising alternative for the management of refractory LS.

Ethical approval

Reviewed and approved by the ''Medicament Research Ethics Committee of the Fundació de Gesció Sanitaria de l'Hospital de la Santa Creu i Sant Pau de Barcelona'' (IIBSP-FOT-2023-122).

Informed consent

All patients signed a written informed consent for the publication of data and/or photographs.

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Conflicts of interest

OY and CM have received transportation assistance from Biofrontera. LM declared no conflicts of interest whatsoever.

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