Clinical Letter

Refractory facial Darier's disease treated with daylight photodynamic therapy

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Dear Editors,

Darier's disease (DD) is an infrequent autosomal dominant skin disorder caused by a mutation of the *ATP2A2* gene on chromosome 12 [1]. Mutations in this gene result in abnormalities in keratinocyte cell-cell adhesion producing an alteration of the keratinization of the skin, which clinically presents with dyskeratotic papules mostly affecting seborrheic and intertriginous areas. Palmoplantar and nail involvement is often present [1–3]. As a wide range of treatments have been proposed for this skin disorder with different results, the management of this disease is still a challenge for the dermatologist.

A woman in her forties, with a medical history of DD diagnosed histopathologically 28 years previously, presented with repetitive flare-ups of coalescent reddish-brown papules and plaques affecting the upper back, forehead, ears, neck and submammary folds. She reported a similar family history for her mother and brother. No other medical history of cutaneous or systemic diseases were reported.

The patient had previously undergone topical therapies with steroids, antibiotics and retinoids and oral intermittent treatment with acitretin and isotretinoin, with poor control of the disease. Daily use of masks due to the COVID-19 pandemic, had also exacerbated midfacial lesions in the patient.

Physical examination revealed itchy erythematous plaques on the midfacial region (Figure 1a), cheeks, cervical region, and submammary folds.

Due to the lack of control of the lesions, off-label use of photodynamic therapy (PDT) was proposed for bothersome facial lesions. Taking the significant facial involvement into consideration, and to enhance tolerance, it was decided to perform daylight photodynamic therapy (dPDT) with methyl aminolevulinate cream. No other corporal areas were treated. After two sessions of dPDT separated by five weeks, complete response was observed in facial lesions, with good tolerance and without recurrence within nine months of follow-up (Figure 1b).

Photodynamic therapy is widely applied to superficial nonmelanoma skin cancers but also to other dermatologic diseases including infectious or inflammatory diseases [4]. Until now, only twelve cases of DD treated with conventional PDT have been reported (Table 1) with promising results. This treatment seems to be effective in both controlling the disease manifestations and preventing recurrences. Clinical response was achieved in nine of twelve patients (75 %) with long-term responses longer than seven months observed in more than 40 % of reported cases.

As the sensation of burn and pain during the treatment is the principal limitation of conventional PDT, its use for large body areas or well-innervated locations such as the face is limited. The efficacy and tolerability of dPDT in treating actinic keratosis is well-known. The shorter period incubation of dPDT promotes a continuous activation of protoporphyrin IX (PPIX), preventing its accumulation in the skin and, consequently, reducing pain during the treatment. That would give to dPDT the advantage of use in treatment

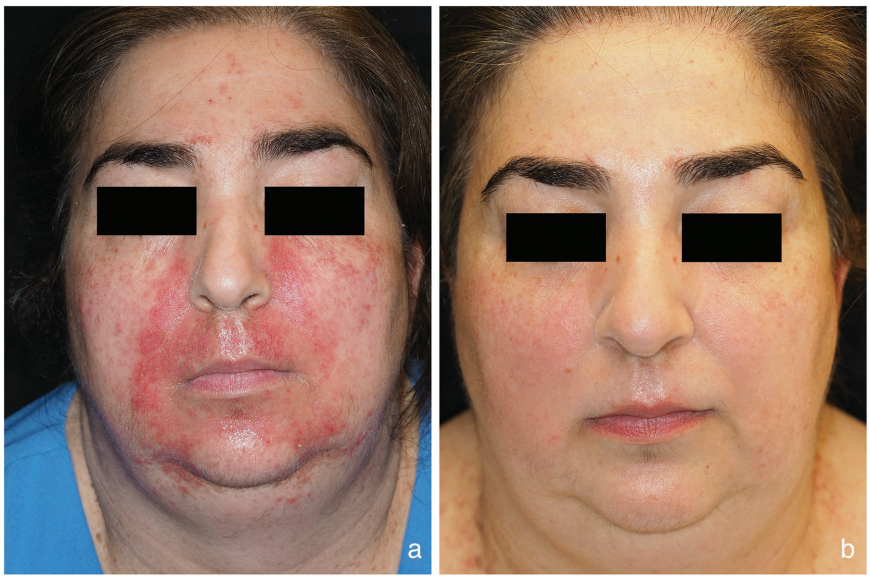

Figure 1 Clinical response observed in facial Darier's disease treated with daylight photodynamic therapy. Macerated, red to brown plaques and papules limited to nasolabial folds, cheeks, chin, and upper lip (a). Complete response achieved after a single session of daylight photodynamic therapy. Clinical response obtained was maintained after eight months of follow-up (b).

Table 1 Main characteristics of Darier's disease cases treated with conventional photodynamic therapy.

	Photosensitizer	Wavelength	Patient number	Treated sites	N° of sessions	Concomitant treatment	Outcome
Avery et al. [2]	MAL	633 nm	1	Left and right neck, submammary and forehead temples	1–2	none	Complete remission No recurrence at 27 months
Amerio P et al. [6]	5-ALA	600–700 nm	2	Back	1	Tretinoin cream 0.05 %	No response and aggravation
			3	Arms	1	Tretinoin cream 0.05 %	Complete remission No recurrence at 3 months
			4	Chest and back	1	Tretinoin cream 0.05 %	Complete remission No recurrence at 3 months
			5	Left arm	1	Tretinoin cream 0.05 %	Partial remission
			6	Back	1	Tretinoin cream 0.05 %	Partial remission
van't Westeinde et al. [7]	5-ALA	420 nm	7	Scalp, retroauricular, face, axillae, submammary	1	none	Exacerbation
Exadaktylou D. et al. [5]	5-ALA	580–740 nm	8	Back, submammary, arms and lateral neck	1	Isotretinoin	Complete remission No recurrence at 3 years
			9	Right buttock	2	Isotretinoin	Partial remission No recurrence at 18 months
			10	Left neck, back and face	2	Acitretin	Partial remission No recurrence at 7 months
			11	Submammary	1	none	Complete remission Minimal recurrence at 18 months
			12	Scalp, retroauricular, face, axillae and submammary	2	Etretinate stopped 3 months after PDT	Recurrence at 6 months or no response
			13	–		–	Did not tolerate the therapy

Abbr.: 5-ALA, 5-aminolevulinic acid; MAL, methyl aminolevulinate.

of large body areas with good tolerance [4]. Another advantage is the homogeneous radiation of irregular surfaces with daylight exposure compared to the light sources used in conventional PDT.

This effect of PDT on DD could be explained by the tissue-specific apoptosis induced by the accumulation of PPIX on acantholytic cells as a result of an increased penetration of the photosensitizing agent and an increased accumulation of exogenous PPIX in the inflammatory cells due to alterations in enzyme activity of heme biosynthesis [2, 4, 5].

Although conventional PDT has been used in a few cases, the use of dPDT for the treatment of DD has not yet been explored. The excellent long-term response and tolerability to dPDT showed in our patient suggests that this modality of PDT could be an especially suitable option for large and recalcitrant DD lesions. More studies are needed to assess the safety and efficacy of this well-tolerated technique for DD.

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Conflict of interest

None.

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