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Milia: An Uncommon Reaction to Photodynamic Therapy☆

Milia, una reacción infrecuente tras terapia fotodinámica

To the Editor:

Photodynamic therapy (PDT) is a noninvasive treatment that combines a light source with a topical photosensitizing agent. The technique is widely used in dermatology for treating certain oncologic conditions such as actinic keratosis and superficial basal cell carcinoma. While PDT is safe and effective, an appreciable number of patients present local adverse effects such as erythema, pain, and edema at the treatment site. Isolated incidents of other adverse effects have been described, including transitory hyperpigmentation, cellulitis, and, more rarely, milia.

A 91-year-old man with skin phototype II on the Fitzpatrick scale and a past history of hypertension and hypertensive heart disease visited our department with lesions in the parieto-occipital region of the scalp. The lesions had appeared 3 years earlier and had not improved despite months of keratolytic therapy. Physical examination revealed multiple soft keratotic crusted papules grouped in the parieto-occipital region of the scalp. Shave biopsy of one of the lesions revealed acanthosis with hyperkeratosis, alternating orthokeratosis and parakeratosis, and focal atypia of keratinocytes in the lower third of the epidermis, confirming the suspected diagnosis of actinic keratosis. PDT was performed using 5-aminolevulinic acid hydrochloride gel (78 mg/g). The area to be treated was covered with an opaque dressing for 3 hours. The area was cleaned using saline solution and exposed to a lamp with red light-emitting diodes at a wavelength of 630 nm (Aktilite CL128, Galderma) and the dosage recommended in the product information sheet (37 J/cm^2). The patient presented considerable erythema in the treated area at the end of the treatment session.

By the follow-up visit a month after treatment, the actinic keratosis had completely resolved; however, multiple millimeter-sized monomorphous, whiteish papules were observed in the treated area (Fig. 1 A). In light of the suspected diagnosis of milia, a 4-mm punch biopsy was performed. The results of histopathology were compatible with milia: multiple cyst-like structures lined by squamous epithelium with a granular layer and containing orthokeratotic keratin (Fig. 2). Treatment was started with 5% salicylic acid in petroleum jelly, applied once daily, and the lesions improved after 2 months of treatment (Fig. 1B).

Milia are small epidermal cysts that present as firm whiteish papules with a diameter of less than 3 mm; they are thought to originate in the pilosebaceous follicle. Cysts are classed as primary milia when they appear spontaneously, predominantly on the face, and as secondary milia[1] when they are caused by trauma or occur in association with inflammatory skin conditions. Secondary milia have been reported in association with second-degree burns, radiotherapy,[2] porphyria cutanea tarda, and after

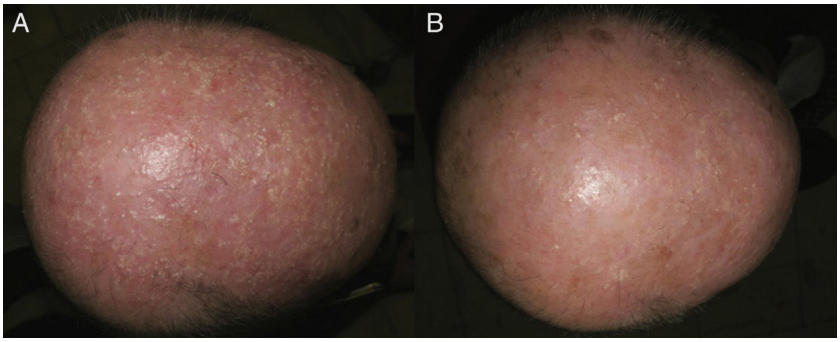

Figure 1 A, Multiple millimeter-sized monomorphous, whiteish papules in the parieto-occipital region. B, Clear improvement of the milia in the parieto-occipital region following application of mild keratolytic agents.

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Table 1 Cases of Milia Following Photodynamic Therapy Published in the Literature.

Cases	Age	Phototype	Disease	Location	Photosensitizing Agent	Incubation Time	Lamp	Dose Regimen	Post-PDT Reaction	Clinical Course and Treatment
Patient 1 Buinauskaite et al.	68	III	AK grade I-II	Parieto-occipital	5-aminolevulinic acid hydrochloride, 20%	4 h	Curelight (PhotoCure)	70 J/cm^2	Not available	Spontaneous remission after 6 months
Patient 2 Buinauskaite et al.	77	III	AK grade I-II	Parieto-occipital	5-aminolevulinic acid hydrochloride, 20%	4 h	Curelight (PhotoCure)	70 J/cm^2	Not available	Spontaneous remission after 6 months
Patient 3 Buinauskaite et al.	84	III	AK grade I-II	Parieto-occipital	5-aminolevulinic acid hydrochloride, 20%	4 h	Curelight (PhotoCure)	100 J/cm^2	Not available	Persistence of milia No treatment
Patient 4 Flores et al.	91	II	AK grade I-II	Parieto-occipital	5-aminolevulinic acid hydrochloride, 7.8% (Ameluz)	3 h	Aktilite CL128 (Galderma)	37 J/cm^2	Erythema	Improvement with 5% salicylic acid after 2 months

Abbreviations: AK, actinic keratosis; PDT, photodynamic therapy.

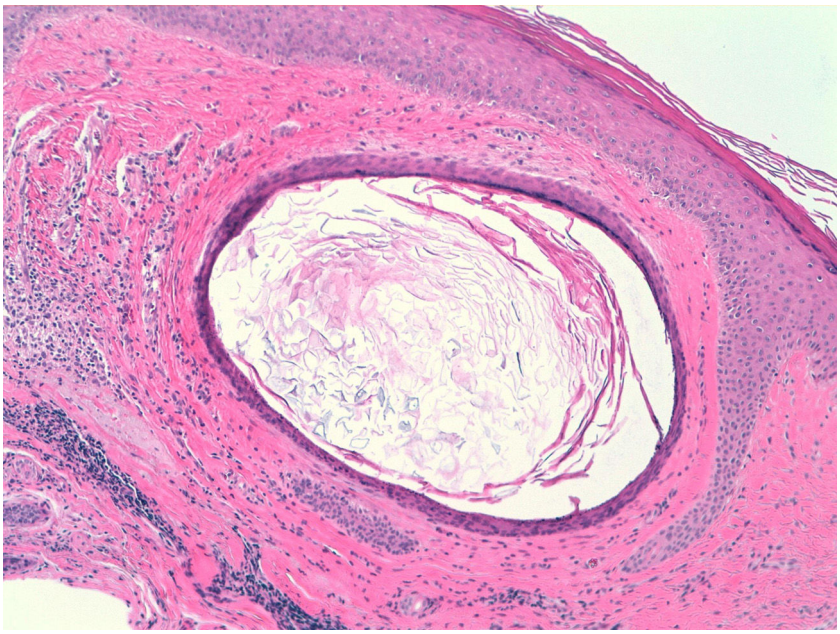

Figure 2 Cyst structure lined by squamous epithelium with a granular and containing orthokeratotic keratin.

tattooing.[3] In our case, the most plausible explanation for the milia may be the intense inflammatory reaction our patient presented during the treatment session.

The appearance of milia following PDT is a rare adverse effect that we had not previously observed in our extensive clinical experience. This phenomenon is known to reflect the severity of phototoxic damage and disruption of the dermal-epidermal junction.[4] Milia have been reported in the literature in 3 patients 3 months after PDT (5-aminolevulinic acid hydrochloride). In 2 of the cases, spontaneous resolution was observed after 6 months[5] (Table 1).

In our case, in contrast to the 3 cases mentioned above, onset of milia occurred earlier and the condition resolved more quickly following keratolytic treatment. This difference may be linked to the severity of the inflammatory reaction our patient presented after treatment. As in the cases mentioned above, the milia appeared following the application of topical 5-aminolevulinic acid hydrochloride in actinic keratosis. No similar reactions have been reported to date in cases in which the photosensitizing agent was methyl aminolevulinate. This phenomenon may be explained by the greater affinity of 5-aminolevulinic acid hydrochloride for cancerous tissue,[6] which leads to greater collateral damage of healthy tissue.

Paradoxically, PDT is one of the most commonly used treatments for milia en plaque.[7]

We present a new case of milia following treatment of actinic keratosis using PDT. The patient had no past personal or family history of milia. Given the benign and potentially self-limiting nature of the condition, it is important for dermatologists to be able to identify milia and avoid mistaking it for treatment failure. In our case, although we explained that the condition was benign, the patient stated that he was unhappy with the cosmetic result and we therefore started mild keratolytic treatment with very good results.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Treatment of a Refractory Venous Ulcer With Terminal Interruption of the Reflux Source☆

Tratamiento de úlcera venosa refractaria mediante la «interrupción terminal de la fuente de reflujo»

To the Editor:

Venous ulcers are the main cause of chronic leg ulcers. They have a high prevalence, high morbidity, and a marked socioeconomic impact. Venous ulcers are frequently encountered in dermatology and vascular surgery consultations, require long-term treatment, and commonly recur.[1] Compressive therapy is the treatment of choice. However, these ulcers can often become chronic and fail to respond to multiple local treatments and dressings. If a significant improvement is not observed within 4 to 12 weeks, conservative treatment is unlikely to result in cure.[2]

We describe the case of a 69-year-old man, with no medical history of interest, who was seen for a painful venous ulcer on the ankle that had appeared 6 months earlier. The patient had undergone conservative treatment with a compressive bandage and local wound treatment, and had twice received oral antibiotic treatment for superinfection. Physical examination revealed an internal inframalleolar ulcer of 4 cm and 2 adjacent incipient lesions (Fig. 1A), as well as varicose veins with secondary dermatosclerosis and skin hyperpigmentation. Triplex ultrasound (3–13-MHz probe) revealed incompetence of the great saphenous vein, with tributaries projecting towards the ulcer bed, and an adjacent incompetent perforator vein. Ultrasound-guided sclerotherapy of the ulcer bed was performed using the terminal interruption of the reflux source (TIRS) technique. In total, the patient underwent 4 sessions at 1-week intervals using a mixture consisting of 1 part 1% polidocanol foam (0.5 mL per session) to 4 parts CO_2O_2 (Tessari method). Complete re-epithelialization was observed by the fourth week (Fig. 1B). The great saphenous vein was simultaneously ablated by intravenous laser (VascuLife, 1470 nm) to treat the proximal reflux and prevent ulcer recurrence. Six months after treatment the patient remains asymptomatic with no lesion recurrence.

Foam sclerotherapy was proposed as a first-line treatment for venous ulcers in 2004.[3] The TIRS technique consists of the treatment of incompetent veins in close proximity to the ulcer bed to generate a sort of internal compressive bandage.[4] At the first consultation Doppler ultrasound is performed to examine the vessels of the ulcer bed and to map the venous system. The target vessels are the incompetent perforators and the incompetent veins of the ulcer bed with continuity with the source of the reflux. Foam sclerotherapy is performed and a compressive bandage applied until the next session. Sessions are carried out at weekly intervals until all incompetent target vessels have been obliterated.

In the cases described in the literature TIRS is effective in almost 90% of cases, with a mean healing time of 4 to 8 weeks.[4,5] We reported comparable outcomes in a series of 6 clinical cases.[6] Compared with conservative treatments or treatment of proximal reflux by sclerotherapy alone, TIRS appears to be a more effective technique, with a shorter healing time.[6–9] The beneficial effects of foam sclerotherapy have also been demonstrated in several studies of large series of patients with long-term follow-up. Because it directly targets the source of the venous ulcer, foam sclerotherapy offers better outcomes than other therapies with low quality of evidence ratings, such as venotonic drugs, stem cells, and growth factors. The risk of recurrence appears to be lower than that reported for the treatment of proximal reflux alone.[4,6,7] However, the importance of compression stockings or bandages in preventing venous ulcers should not be overlooked.

TIRS can be performed on an outpatient basis, and improvements in ulcers and associated clinical signs can be observed within 2 weeks. The most feared complication is accidental perforation of the posterior tibial veins and consequent thrombosis. The most commonly described adverse effects are pain, bruising, and discomfort caused by the bandages applied after treatment. Other less commonly reported complications of sclerotherapy include transient neurological adverse effects, intra-arterial injection and subsequent ischemia, pulmonary thromboembolism, and deep-vein thrombosis.

We believe that TIRS is a promising and safe technique with a minimum recovery time.

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