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LETTER TO THE EDITOR

Granuloma annulare: report of 13 patients treated with photodynamic therapy

Dear Editor,

Granuloma annulare (GA) is a benign inflammatory granulomatous skin.¹ Photodynamic therapy (PDT) has been described as another therapeutic option for localized GA, with a degree of recommendation B.² Therefore, we have carried out a review of all patients with GA treated with PDT in our Dermatology Unit.

We performed a retrospective observational study in San Jorge Hospital (Huesca, Spain) including all patients diagnosed with GA and treated with PDT between 2007 and 2018. Diagnosis of GA was clinical and a skin biopsy was performed if it was necessary. In all patients, methyl aminolevulinic acid (MAL) or aminolevulinic acid (ALA) was applied under occlusive and opaque dressing for 3 h and illuminated with LED 635 nm (Aktelite®, Uppsala, Sweden) with a fluence of 37 J/cm². The lesions were prepared by a soft curettage or microneedling, and some lesions did not receive any kind of prior skin preparation. Continuous variables were described using means and standard deviations. Statistical analyses were carried out using SPSS software (version 20.0; IBM Corp, Armonk, NY, USA).

Thirteen patients were included in the study (Table 1). Eleven cases (84.6%) were women and two men (15.4%), with a mean of 53 years old. Eighty-four per cent patients ($n = 11$) underwent a previous biopsy to confirm the diagnosis of GA. The majority received a pretreatment with curettage (38.5%, $n = 5$) or microneedling (46.2%, $n = 6$). Seven patients (53.8%) responded completely to PDT and four partially improved (30.8%) (Fig. 1). Of the total of responding patients and those who improved, 9 (81.81%) were treated with MAL, 1 (9.09%) with ALA and 1 (9.09%) with both. With regard to the number of sessions, the majority received between one and three sessions separated by four weeks with MAL. Seventy per cent ($n = 9$) tolerated the PDT session quite well, and 30% ($n = 4$) reported moderate pain. Cosmetic result was excellent in all patients with clinical remission, with just a slight hyperpigmentation in two patients who have complete response.

To our knowledge, there are few articles analysing the effectiveness of PDT for GA. The majority are isolated clinical cases^{3,4} or series of clinical cases,^{5,6} and they are summarized in table 1. The largest one was published by Calzavara-Pinton *et al.*⁷ in a retrospective analysis of real-life practice of off-label PDT using MAL.

Compared PDT effectiveness with other treatments, for example intralesional corticosteroids, this obtained complete clearance of 70% of the patients compared with the 44% of placebo.² Concerning cryosurgery, the response rate was 80% with a single freeze-thaw cycle in a clinical trial including 31 patients but cosmetic results with cryosurgery were good only in 11 patients (39.3%) and criostatrophy occurred in four patients (21.1%).⁸

The cellular photodamage after PDT involves different death pathways. The result of MAL-PDT depends on the thickness of corneal layer and epidermis, in inflammatory cutaneous diseases with mononuclear and lymphocytic infiltration.⁷ ALA-PDT has been demonstrated to induce in vivo apoptosis in lesional T-lymphocytes in psoriatic plaques.⁹ The etiopathogenesis of GA is still unknown, but some authors propose that T-helper cells have an interaction with histiocytes and this leads to granuloma formation. In addition, these T cells express interferon gamma and the aggressive macrophages express tumour necrosis factor (TNF- α) and matrix metalloproteinases that contribute to inflammation and destruction.¹ Therefore, to try to obtain a good response and that apoptosis occurs in T-lymphocytes, it is important to pretreat the skin lesion that favours the penetration of the photosensitizer.

In conclusion, the efficacy of PDT in localized GA is similar to other more established treatments and without adverse effects. Until a clinical trial shows its real efficacy, PDT could be considered after failure of other easier and cheaper treatments such as topical or intralesional corticosteroids and maybe before cryotherapy in order to avoid permanent scars.

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Conflicts of interest

The authors have no conflict of interest to declare.

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Table 1 Current and previously reported cases of GA

Author	Num. of patients	Age (average) (years)	Gender (M/F)	Duration of disease (months) (range)	Previous treatment	Location	PDT sessions	Photosensitizer	Outcome	Recurrence and follow up (months)
Kim ³ , 2006	1	25	F	3	–	Hands	4	20% 5-ALA	Complete remission	No recurrence 7
Hanneken ⁴ , 2008	1	40	F	12	Topical corticosteroids	Lower limbs	9-13	20% 5-ALA	Complete remission	–
Weissensteil ⁶ , 2008	7	55	4/3	48 (4-108)	Topical corticosteroids: 100% (n = 7) Ultraviolet treatment: 27.14% (n = 4) Oral corticosteroids: 28.57 (n = 2)	Hands: n = 4 Lower limbs: n = 1 Elbow: n = 1	2.4	20% 5-ALA	Complete remission: 28.57% (n = 2) Improvement: 28.57% (n = 2) No change: 42.85% (n = 3)	– 6
Piaserico ⁵ , 2009	3	53	2/1	80(36–108)	1 patient: Topical corticosteroids and tacrolimus 1 patient: Topical, oral and intralesional corticosteroids, and hydrochloroquine 1 patient: Topical corticosteroids and tacrolimus	Generalized GA	3 (n = 2) 5 (n = 1)	MAL	Complete remission: n = 1 Improvement: n = 2	– 6
Calzavara-Pinton ⁷ , 2012	13	50.8 (±9.8)	5/8	–	–	–	2.8 ± 1.4	MAL	Marked improvement: 53.8% (n = 7) Moderate: 15% (n = 2) No change: 31% (n = 4)	– 7.3 ± 8.4
Garcia-Mallinis, 2020	13	53 (±15)	2/11	24 (1–72)	Topical corticosteroids: 100% (n = 13) Tacrolimus: 23.1% (n = 3) Hydrochloroquine: 15.4% (n = 2) Cryotherapy: 15.4% (n = 2) Pentoxifylline: 30.8% (n = 4) Oral corticosteroids: 38.15% (n = 5)	Hands: 53.9% (n = 7) Lower limbs: 30.8 (n = 4) Upper limbs: 7.7% (n = 1) Trunk: 7.7% (n = 1)	3.15 ± 2.7	MAL: 76.9% (n = 10) 20% 5-ALA: 15.4% (n = 2) Both: 7.7% (n = 1)	Complete remission: 61.5% (n = 8); 53.8% (n = 7) Improvement: 30.8% (n = 4) No change: 15.4% (n = 2)	– 35 ± 25.34

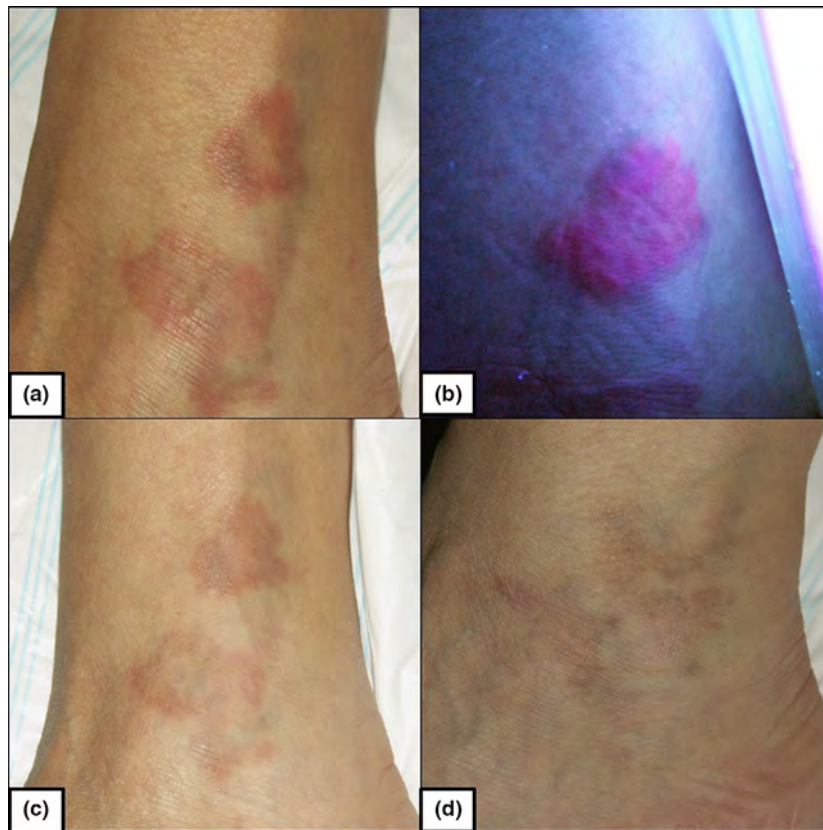


Figure 1 (a) Granuloma annulare (GA) in lower limbs. (b) Fluorescence before photodynamic therapy (PDT) session. (c) Hyperpigmentation 1 month later after two sessions of PDT separated by 4 weeks. (d) Complete resolution of GA

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