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Photodynamic Therapy for Granuloma Annulare: More than a Shot in the Dark

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Key Words
Photodynamic therapy · Granuloma annulare · Side effects

Abstract
Background: Granuloma annulare (GA) is a benign granulomatous and inflammatory skin disorder. The pathogenesis remains enigmatic and convincingly effective treatment options are not available. Inspired by a report showing photodynamic therapy (PDT) to be effective in a single patient with GA, we sought to evaluate this benefit in a series of patients with GA. ***Observations:*** PDT was performed in 7 consecutive patients with histologically confirmed GA located at the extremities. First, 20% ALA gel was applied under an occlusive dressing for 5 h, followed by illumination with 100 J/cm^2 by a standard red-light source. In total, 2–3 PDT sessions were performed, with an interval of 2–4 weeks between each session. Treatment was stopped when complete remission was achieved or when GA lesions remained unchanged after 2 consecutive PDT sessions. The overall response rate was 57%. In 2 patients (29%), GA cleared completely, in 2 patients (29%) the skin lesions improved markedly and in 3 patients (43%) no clinical response could be observed. ***Conclusion:*** These promising results should be evaluated in larger controlled studies. In selected patients, PDT might be a valuable recruit for the sparse armory available to treat GA.

Granuloma annulare (GA) is a granulomatous inflammatory skin disorder with localized or disseminated distribution of the papular lesions. The pathogenesis remains enigmatic and effective treatment options are still missing [1–3]. Various topical and systemic treatment approaches have been shown to be effective only in a minority of patients [1, 2], e.g. topical application of glucocorticoids, ascomycin or vitamin E, PUVA (psoralen and UVA) therapy, systemic use of dapsone, ciclosporine, isotretinoin, fumaric acid esters, allopurinol, TNF-α antagonists and others. As GA is a benign, often asymptomatic, skin disease, the risk-benefit ratio of systemic therapy is poor, and therefore systemic therapy is generally not recommended. Interestingly, remissions may be induced by a skin biopsy of the lesion or can occur spontaneously.

Inspired by a case report showing photodynamic therapy (PDT) to be effective in a patient with GA [4], we sought to evaluate the therapeutic potential of PDT upon GA in a series of patients.

Patients and Methods

Seven consecutive patients (3 women, 4 men; mean age, 55 years) with histologically confirmed disseminated GA (3–12 lesions) from our outpatient clinic were included in this study. None of the patients had diabetes mellitus. The mean duration of GA

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Table 1. Patient data regarding history, histological thickness of GA and PDT

Patient No.	Age/sex	Duration of disease years	Skin type (I–VII)	Previous treatment	Target lesion	Histological depth of lesion mm	PDT sessions	Outcome
1	64/m	2	II	TS,	dorsum of hands	1.3	3	complete remission
2	59/m	5	II	TS, UV	dorsum of hands	n.a.	3	no change
3	74/m	9	III	TS, SS, UV	elbow	1.7	2	improvement
4	50/m	3	III	TS, SS, UV	dorsum of hands	1.2	3	complete remission
5	25/f	4 months	II	TS	lower limbs	1.4	2	no change
6	70/f	4	I–II	TS, UV	dorsum of hands	n.a.	2	improvement
7	56/f	5	II	TS	lower arm	1.0	2	no change

TS = Topical application of glucocorticoids; UV = ultraviolet treatment; SS = systemic glucocorticoids; n.a. = not available.

was 4 years (4 months to 9 years). In each patient, at least 1 conservative treatment modality had been previously ineffective (table 1). The most cosmetically bothersome lesions were chosen, the worst lesion first, as targets for PDT. The GA lesions were located on the dorsum of the hands (4 patients), the lower limbs (1 patient), the lower arm (1 patient) or the elbow (1 patient; table 1).

To begin, 20% 5-ALA gel (5-aminolevulinic acid HCl, 1.0 g; aqua ad injectabila, 1.9 g; dimethyl sulfoxide, 2.0 g; Tylose H 300 ad, 5.0 g) [5] was applied under an occlusive dressing for 5 h, followed by illumination with 100 J/cm^2 by a commercial standard red-light source (Waldmann PDT 1200, 635 nm). To exclude an intrinsic therapeutic effect by the red-light irradiation itself, the contralateral hand in patients with both hands affected (n = 2) was illuminated with red light, i.e. without pretreatment 5-ALA. PDT was performed every 2–4 weeks, up to a total of 3 sessions depending on the lesions' responses. PDT was stopped when the GA lesions cleared or if no clinical improvement could be seen after 2 consecutive PDT sessions.

Results

The side effects during and after PDT were comparable to the common side effects of PDT for other skin diseases, and included mild to strong local pain and inflammatory reactions. The mean pain score, assessed by a visual analog scale (range 0 = no pain to 10 = unbearable pain) immediately after each illumination, was 5.2 (range 0–8) for the first and 4.6 (range 0.5–7.5) for the second PDT treatment. Local cooling was provided during illumination by a commercial cold air flow system (Cryo 5; Zimmer Electronics). Four of the 7 patients took 1 g paracetamol and 30 mg codeine orally 1 h before the PDT session. Local anasthesia with 1% mepivacaine subcutaneously was applied in 3 patients who noticed stronger pain during PDT. The mean pain score was higher in responders to PDT than in nonresponders (5.9 vs. 4.3 at the first PDT session). Shortly after treatment, all patients experienced a mild to severe local inflammation, edema, crust and scaling. Moderate exudation occurred in 1 patient. Within 2 days after PDT, the edema disappeared. Scales and crusts did not persist longer than 2 weeks. A complete clinical remission with a slight transitional hyperpigmentation of the target lesions was achieved in 2 patients (29%; fig. 1). The remission was stable over a 6-month follow-up period. In 2 patients, the skin lesions improved markedly. Improvement was defined as a clinically marked decrease in thickness or a reduction in size of the lesions. One of the patients with significant improvement decided to discontinue PDT because of side effects, i.e. mild local pain and inflammation. In this patient, the PDT-induced improvement was taken to a complete remission by 18 sessions of bath PUVA therapy (cumulative dose 25.5 J/cm^2). In 3 patients, no clinical response could be observed. A histological follow-up was not performed. An average of 3 PDT cycles was required to achieve a complete remission. There was no significant correlation between the outcome of PDT treatment and the patients' sex, skin type, previous treatment modalities or the duration of the disease. The clinical side effects, apart from pain, were independent of the clinical response to PDT. Irradiation with red light alone had no effect on the GA lesions. In 2 patients with both hands affected, only the PDT-treated side healed, while the other hand exposed to only red light remained unchanged. The subsequent treatment of the control side with PDT eventually led to healing of the GA as well.

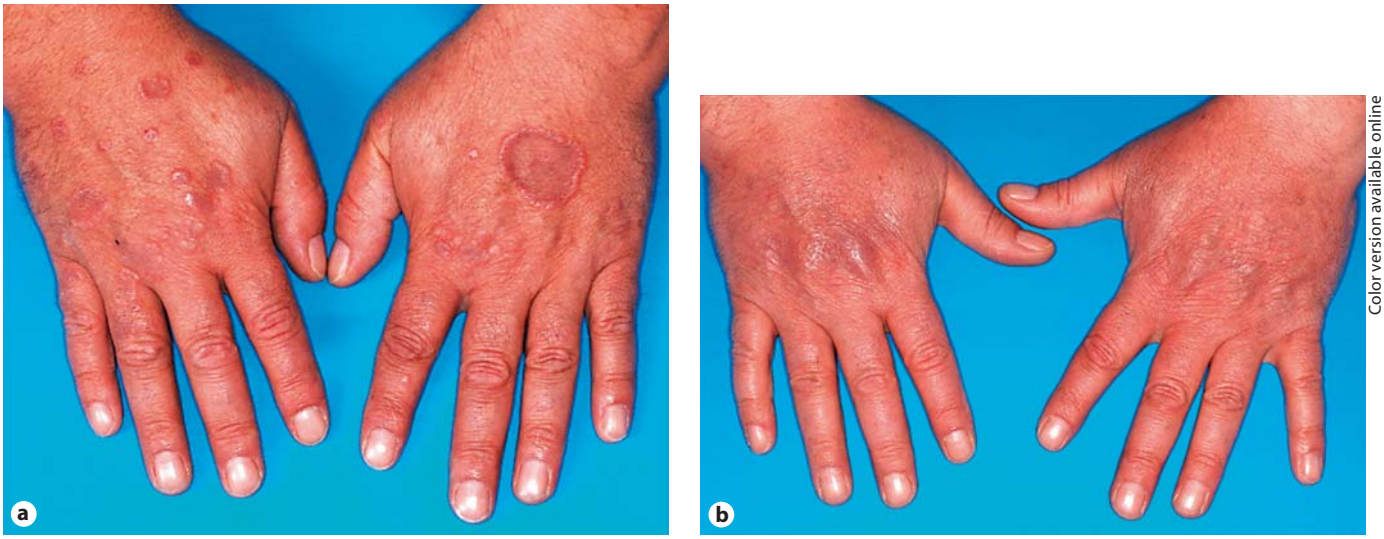

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Fig. 1. a Granuloma annulare at the dorsum of both hands (ring-shaped and disseminated erythematous papules before PDT). **b** Complete remission with hyperpigmentation after three PDT sessions.

Discussion

PDT is a well-established treatment modality for dermato-oncologic disorders such as actinic keratoses, Bowen's disease and superficial basal cell carcinoma. Furthermore, certain benefits of PDT have been reported anecdotally for inflammatory dermatoses, such as localized scleroderma or acne vulgaris [5], as well as for viral warts [6]. A single case report on the efficacy of PDT in GA suggested that PDT might also be a therapeutic option for this often incurable disease. Indeed, in 4 of 7 patients (57%) with therapy-resistant GA, complete healing (2/7) or profound improvement (2/7) could be achieved by PDT, while no effect was observed following illumination with red light alone. The mechanisms responsible for this effect are not yet understood. GA is a granulomatous skin disease characterized by necrobiotic granulomas. Granuloma formation most likely depends on type 1 T helper cells that activate macrophages to coexpress tumor necrosis factor-α and metalloproteinases (MMP-2 and MMP-9) that finally promote matrix degradation [7].

The efficacy of PDT in GA might depend on its ability to induce T cell apoptosis. The penetration of PDT into the epidermis and superficial dermis of the human skin is generally limited to 3 mm. The histological depth of the GA lesions in our patients was 1.7 mm at maximum, measured from the stratum granulosum down to the bottom of the lesion. Thus, all lesions should have been within the scope of PDT. Since the paralesional inflammatory infiltrate may extend from the corium to deeper skin layers, the sensitivity of GA to PDT may depend on the extent and level of granuloma formation throughout the skin. In particular, the deeper or subcutaneous forms of GA may not be sufficiently reached by PDT to achieve healing, which explains the lack of response in 3 of the 7 patients reported here. Hypothetically, solid strands of collagen within the GA may decrease the penetration of red light. However, no relevant differences in the presence and distribution of collagen strands could be noticed histopathologically when comparing responsive and nonresponsive GA lesions.

The side effects during and after PDT were similar to the side effects observed in other indications. This supports the suggestion that cells in the GA lesions had actively metabolized 5-ALA into the photoactive protoporphyrin IX. The pain during PDT for actinic keratosis or basal cell carcinoma usually increases from the first to the second PDT session [8]. However, in our patients, the pain assessed by a visual analog scale decreased from the first to the second PDT session. It is possible, but unlikely, that there might be disease-specific differences regarding the PDT-induced pain course. More likely, this difference might be explained by the varying intervals between the sessions. The usual interval between two PDT sessions for actinic keratosis is between 7 and 15 days. Hence, the second PDT is usually performed while

the inflammation of the treated site – induced by the first session – is still ongoing. This could plausibly explain a certain aggravation in pain levels. If the second PDT is not performed until after 2 weeks have passed, the local inflammation of the first session will have already subsided. In this study, PDT was only performed every 2–4 weeks.

The promising results of the current study have to be evaluated in larger controlled studies. They hold promise that PDT might be a substantial addition to the sparse armory available to treat GA.

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