

SCIENTIFIC LETTER

New approaches to refractory necrobiosis lipoidica with photodynamic therapy: Case report



Nuevos enfoques en la necrobiosis lipóidica refractaria con terapia fotodinámica: caso clínico

Necrobiosis lipoidica (NL) is a rare chronic granulomatous disease of female predominance (3:1) that affects 0.3% up to 1.2% of patients with diabetes mellitus. The median age of onset is typically around the fourth to fifth decades of life, although onset starts earlier in patients with type 1 vs type 2 diabetes and nondiabetics. NL is strongly, but not exclusively, associated with diabetes mellitus. Plaques are violaceous-brown, contain an atrophic central area with yellowish-brown discoloration with telangiectasis and are often found in both lower extremities. Ulceration occurs in up to 35% of patients and is often associated with pain. NL is usually diagnosed through physical examination, yet skin biopsy can help differentiate it from diabetic dermopathy, sarcoidosis, necrobiotic xanthogranuloma or granuloma annulare.^{1,2}

Although the pathophysiology of NL remains unclear, microangiopathy may play a key role in immunomediated vascular disruption leading to collagen degeneration.³ Histopathologically, NL is identified by horizontal palisaded neutrophilic and granulomatous inflammation and collagen degeneration occurring beneath the epidermis, and necrobiosis.⁴

Photodynamic therapy (PDT) is a photochemotherapy based on the local application of a photosensitive compound (5-aminolaevulinic acid or methyl ester 5-aminolaevulinate) and subsequent exposure to a light source of adequate wavelength. Inside target cells, photosensitizers are turned into photoactive protoporphyrin IX (PpIX) and after an incubation period (usually 3 h), PpIX is activated by an artificial light source (conventional PDT) or sunlight (daylight PDT), leading to the production of reactive oxygen species (ROS), which eventually triggers the apoptosis and necrosis of target cells, and the stimulation of an immune modulating response.^{5,6}

We report our initial experience with 2 patients with refractory NL treated with PDT: patient #1 was a 17-year-old woman diagnosed with type 1 diabetes at the age of 6 years (case #1) with no chronic diabetes complications described to date, and currently treated anxiety as the only comorbid-

ity, good metabolic control, and current basal-bolus insulin therapy. The patient presented with an >8-year history of a single plaque with erythematous borders and an atrophic central area with 5 cm × 3 cm telangiectasis on her right leg in the lower pretibial region. Punch biopsy confirmed the presence of NL.

Patient #2 was a 32-year-old previously healthy woman (case #2) who presented with a 6-year history of a single annular plaque with overlying 5 cm × 4 cm hyperpigmented telangiectatic patches on her right leg. A screening test for diabetes and diabetes-associated autoantibodies were performed while on PDT. The results did not show any alterations. Since the 2 patients underwent topical corticosteroids treatment (clobetasol propionate 0.05% cream), along with calcineurin inhibitors (pimecrolimus 1% and tacrolimus 0.1%) with no significant improvement we decided to put them on PDT. The photosensitizer was applied with an incubation period of 3 h under occlusion with 37 J/cm² of red light at a wavelength 630 nm for 10 min. In case #1, 2 cycles of 3 sessions with an interval of 2 weeks between sessions were administered. The 2 cycles were separated by a 1-year interval. Methyl-aminolevulinate (MAL; Metvix x[®], Galderma, Lausanne, Switzerland), a photosensitizer, and Aklilite e[®] CL128 lamp (Galderma, Lausanne, Switzerland) were used. The treatment was highly effective with almost complete resolution of the plaque leaving residual hypopigmentation only (Fig. 1, A and B). In case #2, we administered 2 cycles of 3 sessions with an interval of 6 weeks between sessions. The 2 cycles were separated by a 1-year interval. The photosensitizer applied was ameluz (5-aminolaevulinic acid, Biofrontier laboratory, Leverkusen, Germany) and the lamp used was BF-RhodoLED[®]. At the end of the treatment period, a remarkable improvement with complete response was observed and the Dermatology Life Quality Index (DLQI) dropped 4 points in case #2 (Fig. 1, C and D).

Given the unknown etiology of NL, effective treatment modalities are rare. Topical corticosteroids have been the first-line therapy of NL for decades, but are minimally effective as monotherapy shows improvements in less than half of the cases.¹ Topical calcineurin inhibitors are increasingly used as alternatives or along with topical corticosteroids. Furthermore, topical calcitriol, pentoxifylline, acetylsalicylic acid, dipyridamole, ticlopidine or high-dose nicotinamide are second-line therapies with a low level of evidence. Over the past decade, the use of PDT has shown promising results as second-line therapy for refrac-

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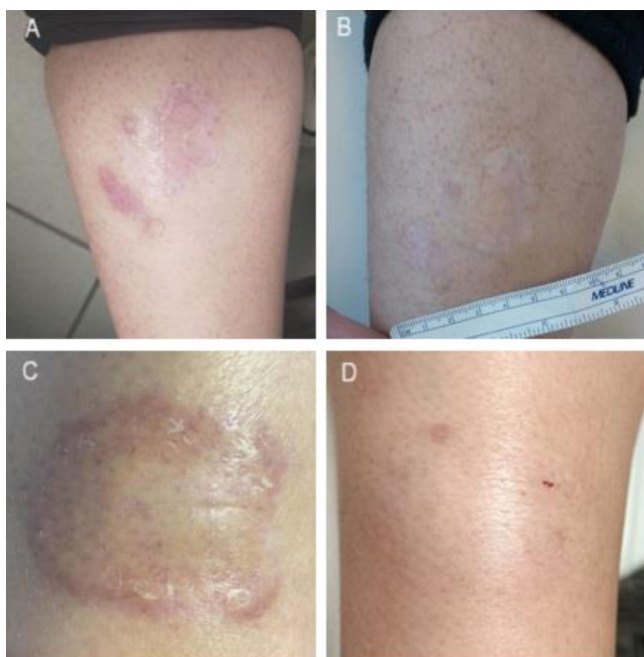


Figure 1 NL lesions in the lower pretibial region: case #1 (A and B, before and after treatment with PDT; case #2 (C and D, before and after treatment with PDT).

tory cases. Medical follow-up is recommended not only because of its recurrent nature but because the appearance of new skin lesions is not a rare finding.

PDT is a non-invasive therapeutic procedure widely used in adult patients for the management of tumoral, inflammatory, and infectious skin diseases. In this article we reviewed our own experience with the use of off-label PDT as a second-line therapy to treat refractory cases of NL.⁵

Kaae et al. (2018) conducted a retrospective study on 65 NL patients treated with PDT and saw complete response in 66% of cases, with similar rates between C-PDT and DL-PDT.⁷

Recently, the PDT technique has been used with daylight for the management of NL. López Sanz P et al. reported 1 case which resolved completely, yet with areas of residual hypopigmentation.⁸

Summarizing the literature search, we find case series that report an overall response rate of 39% up to 100%.^{9,10}

The wide variety of results could be explained by the heterogeneity of the lesions, exposure time, number of cycles, periodicity between sessions, the energy applied, and the concentration of the drug.³

In conclusion, the management of NL can be challenging for diabetologists and dermatologists alike. It is remarkable how PDT could increase the success rate. Our experience shows variable but promising responses vs previous conventional therapies. However, there are no clinical trials, reports with a high level of evidence, or guidelines on the management of NL.

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Authorship

The authors declare that all authors have read and approved the manuscript and that the requirements for authorship have been met. Each of the people who appear as the author of the article has participated in a relevant way in the design and development of it to assume responsibility for the contents and, likewise, agree with the final version of the article.

Originality of the material

The authors declare that the content of the article is original and that it has not been previously published nor is it submitted or submitted for consideration to any other publication, in whole or in part.

Informed consent

Patient data does not identify the subject. Informed consent has been obtained from the patient authorizing its publication, reproduction and dissemination on paper and on the Internet in Primary Care.

The authors declare that the protocols established by the health center have been followed to access the data from the medical records in order to be able to make this type of publication for dissemination purposes to the scientific community.

Conflict of interest

None declared.

References

1. Nihal A, Caplan AS, Rosenbach M, Damsky W, Mangold AR, Shields BE. Treatment options for necrobiosis lipoidica: a systematic review. *Int J Dermatol*. 2023;62:1529–37.
2. Hashemi DA, Brown-Joel ZO, Tkachenko E, Nelson CA, Noe MH, Imadojemu S, et al. Clinical features and comorbidities of patients with necrobiosis lipoidica with or without diabetes. *JAMA Dermatol*. 2019;155:455–9.
3. Rajabi-Estarabadi A, Divya, Aickara J, Hirsch M, Williams NM, Maranda EL, et al. Laser and light therapies for the treatment of necrobiosis lipoidica. *Lasers Med Sci*. 2021;36:497–506. Available from: <https://doi.org/10.1007/s10103-020-03147-3>
4. Asai J. What is new in the histogenesis of granulomatous skin diseases? *J Dermatol*. 2017;44:297–303.
5. Di Bartolomeo L, Altavilla D, Vaccaro M, Vaccaro F, Squadrito V, Squadrito F, et al. Photodynamic therapy in pediatric age: current applications and future trends. *Front Pharmacol*. 2022;13:1–18.
6. Gilaberte Y, Serra-guillén C, Elena M, Heras D, Ruiz-rodríguez R. Terapia fotodinámica en dermatología. 2006;97:83–102.
7. Kaae J, Philipsen PA, Wulf HC. Photodynamic therapy of necrobiosis lipoidica using methyl aminolevulinate: a retrospective follow-up study. *Photodiagn Photodyn Ther*. 2018;22:223–6. Available from: <https://doi.org/10.1016/j.pdpdt.2018.04.020>.
8. López Sanz P, Faura Berruga C, Guerrero Ramírez C, Manso Córdoba S, Alfaro Martínez ME, García Vázquez A. Daylight photodynamic therapy in necrobiosis lipoidica: a

promising treatment? *Photodermatol Photoimmunol Photomed*. 2023;39:294–5.

9. Bernia E, Llombart B, Bancalari B, Diago A, Serra-Guillén C. Conventional photodynamic therapy for necrobiosis lipoidica: successful treatment in a series of 4 cases. *Actas Dermosifiliogr*. 2020;111:605–8. Available from: <https://doi.org/10.1016/j.ad.2019.01.022>
10. Truchuelo T, Alcántara J, Pérez B, Jaén P. Photodynamic therapy for necrobiosis lipoidica is an unpredictable option: three cases with different results. *Int J Dermatol*. 2013;52:1589–90.

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