Successful Treatment of Necrobiosis Lipoidica Diabeticorum With Photodynamic Therapy

Michael Heidenheim, MD; Gregor B. E. Jemec, MD, DMedSci; Department of Dermatology, Roskilde Hospital, Roskilde, Denmark

The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 60-year-old white woman was seen at our clinic with a 10-year history of 4 asymptomatic progressive shiny patches on the right lower leg. The patient also had type 1 diabetes mellitus that was well controlled and had been so throughout the period; in addition to daily insulin, the only medication used was a nonsteroidal anti-inflammatory drug to treat symptoms of arthrosis. She had never received skin grafts; had no ulceration, deep venous thrombosis, or cellulitis; had never undergone a surgical procedure; and had never experienced trauma to the legs. The patches were initially red to brown, but 2 had progressed to yellow, slightly atrophic plaques, and 2 lesions had enlarged to a diameter of 5 to 6 cm with prominent red borders. Physical examination revealed annular, well-circumscribed erythematous plaques with waxy, telangiectatic centers and slightly elevated red borders. None of the lesions had ulcerated (Figure 1). Analysis of a biopsy specimen confirmed the diagnosis of necrobiosis lipoidica diabeticorum (NLD).

THERAPEUTIC CHALLENGE

Necrobiosis lipoidica belongs to the idiopathic cutaneous palisading granulomatous dermatitides associated with a degeneration of collagen, and is most often seen on the legs and often occurs in patients with diabetes mellitus. The disease may lead to skin atrophy, which may be aggravated by topical or intralesional treatment with corticosteroid agents, which constitute the most widely used therapy. Likewise, systemic glucocorticosteroid agents may induce skin vulnerability and elevated serum glucose levels, which contraindicated the use of this drug in our patient with diabetes. Alternatively, psoralen plus UV-A was considered usable, but because of risk of hyperpigmentation and bullous lesions, the patient declined this option.

Treatment with high-potency topical mometasone furoate 0.1% (Elocon; Schering Corp, Kenilworth, NJ) and clobetasol propionate (Dermovat; GlaxoSmithKline, Research Triangle Park, NC) and systemic antioxidant therapy with ascorbic acid and vitamin E for 6 months was ineffective. Likewise, cryotherapy, a series of radiotherapy using grenz rays, and a 3-month trial of systemic allopurinol therapy were discontinued because of lack of response.

Because successful treatment options for NLD seemed limited, we initiated a regimen of photodynamic therapy (PDT) using methyl aminolevulinate (Metvix; Photocure ASA, Oslo, Norway) as a topical photosensitizer and an incoherent red-light source. In a previously published study,1 PDT appears to have an anti-inflammatory effect as well as a tissue-conserving effect.

SOLUTION

Photodynamic therapy was initiated with 632 nm of red-light (CureLight 2; Photocure ASA; 37 J/cm² [light-emitting diodes, 580-670 nm], peak wavelength at 631 nm) activation of methyl aminolevulinate applied to the histologically verified NLD lesion. The procedure included application of methyl aminolevulinate (160 mg/g) under adhesive bandage occlusion for 3 hours to the NLD lesion before exposure to red light. The illumination was administered for 8 minutes and was tolerated without the use of local or systemic analgesia.
During 3 treatments given 1 week apart, a marked reduction in size and color of the lesion was noted, and after a further 3 treatments administered at the same intervals the lesion disappeared clinically and histologically (Figure 2). Findings at 24-month follow-up suggest an ongoing stabilized remission status.

**COMMENT**

Necrobiosis lipoidica diabeticorum is a skin disease that is usually difficult to treat. The evidence base of all therapy is limited. One clinical trial, which tested the use of aspirin therapy, reported negative results. First-line therapy for NLD includes nonsteroidal inflammatory agents, cryotherapy, and potent topical glucocorticoid agents for early lesions and intralesional corticosteroids injected into the active borders of established lesions. Systemic glucocorticoid therapy may also be effective but can be associated with adverse effects in patients with diabetes. Other therapies for NLD are used in an attempt to decrease the microangiopathy and vascular thrombosis by increasing fibrinolysis or decreasing platelet aggregation and thromboxane A2 synthesis. Anecdotal reports include uncontrolled NLD case series mention stanozolol, inositol niacinate, nicofuranose, ticlopidine hydrochloride, pentoxifylline, retinoids, cyclosporin, chloroquine, fumaric esters, psoralen plus UV-A, and allopurinol as treatment options; however, these treatments are only marginally effective in most patients. No major randomized controlled trials are available to identify best clinical practice.

Photodynamic therapy is mediated by oxygen-dependent photochemical reactions. On absorption of photons of light, the photosensitizer is excited to a short-lived singlet state followed by transition to the reactive triplet state. From its triplet state, in the presence of oxygen, reactive free radicals and singlet oxygen species ensue. These, in turn, react with cell membranes, causing direct damage to the mitochondria, endoplasmic reticula, or plasma membranes. Some indirect effects may also occur in the normal microvasculature and in the inflammatory and immune host system. The most common adverse effect of PDT is pain, burning, or stinging at the site of treatment, although most patients, like ours, do not request pain relief.

Photodynamic therapy is a well-established treatment mainly used for dermato-oncologic conditions. By using noncoherent and coherent light sources on a photosensitizer, such as the heme precursor 5-aminolevulinic acid or its methyl ester (methyl aminolevulinate), to induce photosensitizing porphyrins, light and oxygen cause photochemical tissue destruction and immunomodulation. This suggests that the off-label use of PDT might be an effective treatment option for a range of inflammatory dermatoses, such as localized scleroderma, acne rosacea, and psoriasis. Photodynamic therapy has also been suggested for photorejuvenation of UV-light damaged skin.

Necrobiosis lipoidica diabeticorum may undergo spontaneous remission with or without residual cutaneous atrophy and scarring, which develops over a longer period. Our patient had stable disease before PDT, with total regression of the lesions after initiation of PDT. Furthermore, regression occurred without atrophy and obvious scarring. This suggests that spontaneous remission was not a probable explanation for our observation.

The immunologic effects of PDT include the production of interleukin 1β, interleukin 2, tumor necrosis factor α, and granulocyte colony-stimulating factor. These factors may have a role in the inflammatory or metabolic changes in NLD, but the exact mechanism has yet to be elucidated.

Topical PDT using methyl aminolevulinate seems to offer a practical noninvasive therapy option for NLD conditions, with the potential for high efficacy and good cosmesis. However, controlled clinical trials are needed to demonstrate more fully the effectiveness of PDT in inflammatory skin diseases.

Accepted for Publication: April 28, 2006.

Correspondence: Michael Heidenheim, MD, Department of Dermatology, Roskilde Hospital, Koegevej 4-7, 4000 Roskilde, Denmark (rsmihed@rak.dk).

Author Contributions: Study concept and design: Heidenheim and Jemec. Acquisition of data: Heidenheim and Jemec. Analysis and interpretation of data: Heidenheim and Jemec. Drafting of the manuscript: Jemec.

Critical revi-
Clinicians, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Manuscripts should be prepared double-spaced with right margins nonjustified. Pages should be numbered consecutively with the title page separated from the text (see Instructions for Authors for information about preparation of the title page). Clinical photographs, photomicrographs, and illustrations must be sharply focused and submitted as separate JPEG files with each file numbered with the figure number. Material must be accompanied by the required copyright transfer statement (see Instructions for Authors). Preliminary inquiries regarding submissions for this feature may be submitted to George J. Hruza, MD (ghruza@aol.com). Manuscripts should be submitted via our online manuscript submission and review system (http://manuscripts.archdermatol.com).