UV-A1 Phototherapy Improves Nephrogenic Fibrosing Dermopathy

Reza Kafi, MD; Gary J. Fisher, PhD; Taihao Quan, PhD; Yuan Shao, PhD; Rui Wang; John J. Voorhees, MD; Sewon Kang, MD; University of Michigan Medical Center, Ann Arbor

A 47-year-old woman presented with a 2-month history of progressive tightening of the skin on her legs. The tightening of her skin had begun 2 weeks after she was hospitalized for acute renal failure precipitated by therapy with nonsteroidal anti-inflammatory drugs. She had no history of renal disease or medical conditions that would predispose her to the organ failure. During her hospitalization, she was treated with supportive therapy only and did not require hemodialysis or peritoneal dialysis. Her renal function normalized, but the skin fibrosis continued to worsen. We initially examined her approximately 2 months after the onset of her skin disease. At the time, she had orange-red indurated plaques on both thighs and the lower part of her legs. The range of motion of her knees was diminished so much that ambulation had become difficult. She denied any signs or symptoms of photosensitivity, Raynaud symptom, or esophageal dysfunction. Serologic evaluation included anti-Scl 70, anti-Sm, anti-ribonucleoprotein, anti-Ro, anti-La, and serum protein electrophoresis, the results of which were all negative. A skin biopsy specimen from an affected area revealed diffuse fibroblastic proliferation, with increased collagen and mucin in the dermis. These changes were consistent with nephrogenic fibrosing dermopathy (NFD).1

The etiology of NFD is currently unknown, and no therapy has been shown to effectively treat this disorder. A marked increase in fibroblastic cells interspersed in thickened dermal collagen bundles1,2 suggests a state of pathologically heightened procollagen synthesis.

We previously reported that UV irradiation efficiently inhibits procollagen synthesis in human skin in vivo.3 UV-A1 (340-400 nm) represents the longest segment of UV spectrum (290-400 nm), with a negligible capacity to cause sunburn in humans. It inhibits procollagen I and III synthesis in cultured human fibroblasts (G.J.F., unpublished data, 2002). Therefore, we hypothesized that UV-A1 phototherapy, by decreasing collagen synthesis, would safely soften the fibrotic lesions of NFD. An investigational treatment protocol to use UV-A1 in NFD was approved by our institutional review board. Our patient gave signed informed consent before receiving the phototherapy.

UV-A1 irradiation to the affected areas occurred 3 times per week for 12 weeks (130 J/cm² every session). A modified Rodnan score, a quantitative scale of skin induration, showed a marked improvement after 12 weeks of phototherapy. A skin biopsy specimen from the treated area revealed a reduction in the number of fibroblasts and a decrease in collagen and mucin in the dermis.

Figure 1. Nephrogenic fibrosing dermopathy of the lower extremities before (A) and after (B) UV-A1 therapy. Pebble undulated surface at baseline is less apparent after 12 weeks of phototherapy. This improvement in clinical appearance was associated with a marked improvement in skin induration. UV-A1 also induced a tanning response in the treated area.
tion ranging from 0 to 3, was determined throughout the study to assess clinical improvement. Softening of the patient’s skin lesions was first noted during the second week of therapy, with a decrease in the modified Rodnan score from 3 to 2. Marked clinical improvement continued throughout the course of therapy, with a final modified Rodnan score of 1 in the affected areas (Figure 1). Improvement in the skin induration was accompanied by an increase in the range of motion of the knees. The patient tolerated the phototherapy well, with no incidence of sunburn or other adverse events. She was followed up for 4 months after cessation of treatment, with no reappearance of skin lesions.

Four-millimeter punch biopsy specimens of the skin were obtained from an involved site before and after the 12-week course of UV-A1 treatment. A biopsy specimen was also obtained from clinically normal, uninvolved skin. Compared with the uninvolved skin, the NFD skin was 35% thicker in the dermal layer, with an almost 2-fold increase in the total collagen content (as measured by hydroxyproline level according to the method of Bank et al (Figure 2A)).

Compatible with these findings, we found that procollagen I and procollagen III messenger RNA (mRNA) levels (as measured by real-time quantitative reverse transcription polymerase chain reaction [PCR] analysis) were substantially elevated (9-fold and 10-fold, respectively) in involved skin compared with uninvolved skin (Figure 2B). Elevated levels of transforming growth factor β1 and connective tissue growth factor mRNA levels in the lesional skin (Figure 2C) indicate that the pathogenesis of NFD may involve excessive signaling by these 2 profibrotic cytokines. Twelve weeks of UV-A1 treatment normalized the elevated mRNA levels of transforming growth factor β1, connective tissue growth factor, and procollagen I and III in NFD skin to those in uninvolved skin (Figure 2, B and C). Consistent with these data, immunostaining of NFD skin with SP-1, a monoclonal antibody directed against procollagen I, was also reduced with UV-A1 treatment (Figure 3). The apparent decrease in the number of fibroblasts may simply be a reflection of procollagen loss (inhibition of synthesis) and/or actual loss of fibroblasts (apoptosis). It was not possible to distinguish between these 2 possibilities in our study. Finally, the clinical improvement that was observed after 12 weeks of UV-A1 treatment correlated with normalization of the total collagen content and dermal thickness in NFD (Figure 2A).

LABORATORY METHODS

HYDROXYPROLINE MEASUREMENT

Reverse-phase high-performance liquid chromatography determination of hydroxyproline levels in skin biopsy specimens was performed according to the method of Bank et al. Hydroxyproline was separated using a commercially available 5-µm reverse-phase column (4.6 x 150 mm) (SphereClone ODS[2]; Phenomenex, Torrance, Calif). Detection of 9-fluorenylmethyl chloroformate derivatized hydroxyproline was performed with a fluorescence detector (1046A; Hewlett Packard Co, Palo Alto, Calif) set at an excitation wavelength of 254 nm and an emission wavelength of 630 nm.

RNA ISOLATION AND QUANTITATIVE REAL-TIME REVERSE TRANSCRIPTASE–PCR

Commercially available kits were used to extract total RNA from skin biopsy specimens (RNaseasy Mini Kit; Qiagen, Chatsworth, Calif) and to perform reverse transcriptase (Taqman Reverse Transcription Kit; Applied Biosystems, Foster City, Calif). A premix (Taqman Universal PCR Master Mix Kit; Applied Biosystems) and a sequence detector (7700 Sequence Detector; Applied Biosystems) were used for real-time PCR analysis. The PCR primers and probes were produced by a custom oligonucleotide synthesis service (Applied Biosystems). Target gene mRNA levels (number of
Nephrogenic fibrosing dermopathy is a newly described fibrosing disorder of the skin that occurs in patients with renal disease. Since its original description, NFD has been reported in 49 patients from Europe and the United States. Initially, all of the affected patients were recipients of hemodialysis, but subsequently, NFD has been diagnosed in individuals who were not receiving dialysis. In one series, the latter group represented 7% of patients with NFD. Cutaneous findings of NFD consist of indurated erythematous plaques on the extremities and trunk, with a characteristic "cobblestoned" or "peau d'orange" appearance. Histologically, there is a marked proliferation of dermal fibroblasts and dendritic cells. The pathologic abundance of collagen appears to be responsible for the thickened and hard skin of NFD.

Although NFD shares some similarities with scleromyxedema, the 2 entities are distinct from one another. In contrast to scleromyxedema, NFD typically involves the trunk and limbs, sparing the head and neck. Also, patients with NFD, unlike those with scleromyxedema, do not demonstrate the presence of monoclonal paraproteins or signs of systemic disease as a result of mucin deposits in vital organs.

The results reported herein support our hypothesis that UV-A1 can effectively be used to treat NFD. UV-A1 efficiently normalized pathologically increased procollagen synthesis, at least in part, through reducing the expression of the profibrotic cytokines, transforming growth factor β1, and connective tissue growth factor. We believe that this process is responsible for the improvement in NFD. UV-A1 phototherapy is the first reported modality to show effectiveness in the treatment of this newly discovered disorder. We doubt that UV-A1 has specificity for NFD, but rather it is possible that treatment with UV-A1 may improve skin fibrosis caused by several different diseases or trauma.

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REFERENCES


Correspondence: Sewon Kang, MD, Department of Dermatology, University of Michigan Medical Center, 1910 Taubman Ctr, Ann Arbor, MI 48109 (e-mail:swkang@med.umich.edu).

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Submissions

Clinicians, local and regional societies, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Submit 4 double-spaced copies of the manuscript with right margins nonjustified and 4 sets of the illustrations. Photomicrographs and illustrations must be clear and submitted as positive color transparencies (35-mm slides) or black-and-white prints. Do not submit color prints unless accompanied by original transparencies. Material should be accompanied by the required copyright transfer statement, as noted in “Instructions for Authors.”

Material for this section should be submitted to George J. Hruza, MD, Laser and Dermatologic Surgery Center Inc, 14377 Woodlake Dr, Suite 111, St Louis, MO 63017.