Successful Treatment of Toenail Onychomycosis With Photodynamic Therapy

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

Although recent progresses in oral antifungal agents have made it possible to treat onychomycosis effectively, these drugs can have considerable adverse liver or kidney effects and medication interactions in special populations such as children, the elderly, and patients with underlying systemic diseases. We describe 2 patients with toenail onychomycosis who were sucessfully treated with photodynamic therapy (PDT).

REPORT OF CASES

CASE 1

An 80-year-old Japanese woman presented with a 3-year history of asymptomatic alterations of the toenails of her right foot. She also had Sjögren syndrome, which was well controlled. She had been diagnosed as having onychomycosis and had been treated with topical terbinafine for 2 years, without success. She did not take any oral antifungal agents because of her advanced age. Physical examination revealed white patches on the surface and distal undersurface of her first to third toenails, without other alterations (**Figure**, A). Direct microscopic examination of superficial nail scrapings with a potassium hydroxide preparation (KOH) revealed branching hyphae. A diagnosis of distal and lateral subungual onychomycosis was made.

CASE 2

A 31-year-old Japanese woman presented with a more than 10-year history of a whitish toenail on her left foot. One year before consultation, she had been treated with oral itraconazole, but the treatment had been discontinued because of gastric pain. Physical examination revealed subungual hyperkeratosis, a yellowish discoloration, and onycholysis in the distal area of her left great toenail. Direct microscopic examination of subungual debris with KOH revealed branching hyphae. A diagnosis of distal and lateral subungual onychomycosis was made.

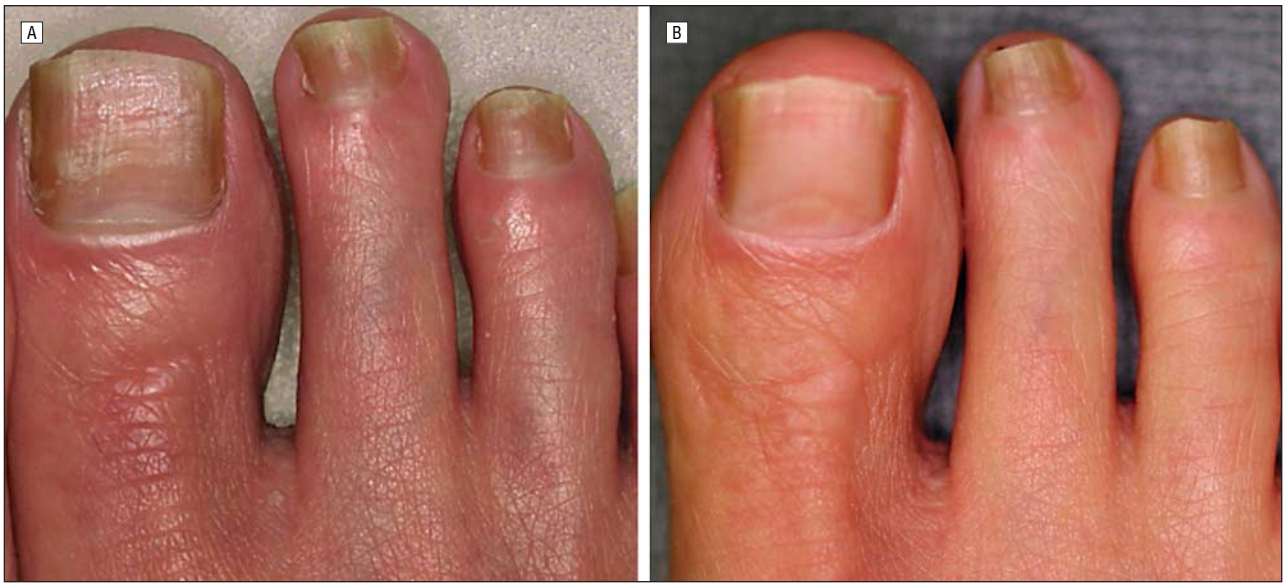

Figure. Case 1. Onychomycosis of the right foot. A, Before treatment, white patches on the surface of the first to third toenails, without other alterations. B, After photodynamic therapy with 5-aminolevulinic acid, the lesion of the first toenail substantially improved. No dermatophyte was detected on potassium hydroxide preparation or culture. The second and third toenails, which were used as controls (second toenail, application of 5-aminolevulinic acid only; third toenail, irradiation only), did not show clinical improvement after treatment.

THERAPEUTIC CHALLENGE

Onychomycosis is a fungal infection of the toenails and fingernails that results in thickening, discoloration, and splitting of the nails, as well as lifting of the nails from the nail bed. The disease, which is caused by dermatophytes, has a high incidence within the general population, especially among older individuals. Multiple therapies, including surgical, chemical, topical, and oral methods, have been described for the treatment of onychomycosis. Generally, oral therapies result in better outcomes. However, none of these treatment options provides lasting high cure rates.

SOLUTION

Photodynamic therapy using 5-aminolevulinic acid (ALA) was administered to our patients. First, a 20% urea ointment (Keratinamin; Kowa Pharmaceuticals, Nagoya, Japan) was generously applied directly to the diseased nail surface and covered with a piece of plastic film wrap for 10 hours. Then, a 20% solution of ALA methyl ester (Sigma-Aldrich Corp, St Louis, Missouri) in aqueous cream (Japanese Pharmacopoeia, Merck Hoei Ltd, Osaka, Japan) was applied to the treated nails, which were sealed with a piece of plastic film wrap and covered with aluminum foil to shut out the light for 5 hours. Before PDT, ALA-induced protoporphyrin IX fluorescence in the nail was confirmed by UV irradiation. The fluorescence was observed at the base of the nail and at the periphery of the onychomycosis lesion. The production of protoporphyrin IX was also confirmed by spectrophotometer. Subsequently, the treatment site, including proximal and lateral nail folds, was irradiated both horizontally and vertically with pulsed laser light at a wavelength of 630 nm at 100 J/cm^2 using an excimer-dye laser (Hamamatsu Photonics KK, Hamamatsu, Japan). 5-Aminolevulinic acid PDT was performed once a week. Both patients had a feeling of some pain during irradiation, but it was tolerable and disappeared within a day.

In case 1, the right first toenail was irradiated 7 times (total dose, 700 J/cm^2). After the irradiation, the lesion substantially improved. No dermatophyte was detected on KOH or on culture. The second and third toenails, which were used as controls, received only ALA or irradiation, respectively. They did not show clinical improvement after treatment (Figure, B). No recurrence was observed clinically at a 6-month follow-up visit.

In case 2, the right first toenail was irradiated 6 times (total dose, 600 J/cm^2). After PDT, the patient's lesion substantially improved, and no dermatophyte was detected by KOH or by culture. No recurrence was observed clinically at a 3-month follow-up visit.

COMMENT

Onychomycosis, which is the most common disease of abnormal nails, is characterized by fungal invasion of the nails. The prevalence of onychomycosis has been estimated at 6.48% in Canada[1] and at more than 10% in Japan.[2] Besides having a high worldwide prevalence, onychomycosis is a public health concern because of its potential for the spread of fungal elements to others. Recent progresses in antimycotic agents, especially oral antifungal agents, have made it possible to treat onychomycosis effectively, but these drugs cannot control and cure onychomycosis in 100% of the cases. Moreover, they may have considerable adverse liver or kidney effects and medication interactions in special populations such as children, the elderly, and patients with underlying systemic diseases such as diabetes, chronic hepatitis, and immunocompromised hosts.

Topical ALA PDT, which is a well-established treatment in dermatology, has proved to be a useful treatment for a variety of malignant skin tumors and inflammatory diseases.[3] Moreover, PDT for several infective viral and bacterial skin diseases has been investigated both in vitro and in vivo.[4-6] In cases involving superficial fungal infections of the skin, several in vitro studies have demonstrated the effectiveness of PDT against cultured *Trichophyton rubrum* in suspension culture.[7-9] Recently, Smijs et al[10] reported the effectiveness of PDT for *T rubrum* infection in an ex vivo human skin model. In light of these findings, we used ALA PDT for the treatment of onychomycosis.

For PDT to be effective against onychomycosis, it is important to apply sufficient concentrations of ALA within the nail matrix and the nail bed. In a previous ex vivo study, the topical administration of ALA onto an excised human nail did not achieve sufficient ALA concentrations, even after a 24-hour patch application.[11] For effective administration of ALA, we applied an occlusive dressing with urea ointment onto the diseased nail before ALA application. Urea ointment has been used for the treatment of onychomycosis to remove the diseased nail and to improve the effect of topical antifungal agents.[12,13] Moreover, electron microscopy has shown that the use of urea ointment can cause structural disintegration of the corneocyte.[14] In our study, the ALA concentration in the treated nail was not measured, but we were able to confirm the absorption of ALA and the production of protoporphyrin IX in the nail using UV irradiation and spectrophotometry. Our results indicated that urea ointment facilitates the penetration of ALA into the nail. The difficulty in treating onychomycosis also results from the deep-embedded nature of the infection within the nail unit. Therefore, the use of an excimer-dye laser might be appropriate because the laser has been shown to reach a depth of at least 15 mm in skin tumors in mice.[15] The longitudinal coverage of the laser is sufficient for treating the nail bed lesion.

To our knowledge, there is no optimal PDT regimen for onychomycosis to date. In our study, we decided to use an irradiation dose of 100 J/cm^2 per treatment based on several in vitro antifungal PDT studies.[7-9] The optimal number of times for PDT also remains unclear, but in our 2 cases, we continued PDT until the patients' lesions clinically improved, and then we confirmed the disappearance of the dermatophytes by KOH and culture.

Although suitable modifications of the application and light source of the photosensitizers will be needed, our results indictate that PDT may be a viable alternative for treating onychomycosis, especially in elderly, compromised, and hepatopathic patients.

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Author Contributions: Dr Matsumoto had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Akita, Tamada, and Matsumoto. *Acquisition of data:* Kawamura and Masuda. *Analysis and interpretation of data:* Watanabe and Tamada. *Drafting of the manuscript:* Watanabe, Kawamura, Masuda, and Akita. *Critical revision of the manuscript for important intellectual content:* Watanabe, Tamada, and Matsumoto. *Study supervision:* Tamada and Matsumoto.
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Submissions

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 [http://archderm.ama-assn.org/misc/ifora.dtl] for information about preparation of the title page). Clinical photographs, photomicrographs, and illustrations must be sharply focused and submitted as separate JPG files with each file numbered with the figure number. Material must be accompanied by the required copyright transfer statement (see authorship form [http://archderm.ama-assn.org/misc/auinst_crit.pdf]). 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).