Treatment of Cutaneous Leishmaniasis With Photodynamic Therapy

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

Old World cutaneous leishmaniasis, which is found in widely scattered parts of Asia, Africa, and Europe, is the result of leishmanial infection of dermal macrophages. Leishmania major is the most common cause of cutaneous leishmaniasis in the Middle East. The cutaneous lesions occur at the site of the Phlebotomus sandfly bite and within a few months develop from small erythematous papules to larger dusky granulomatous lesions, often with ulcerated centers and raised indurated borders. The lesions may heal spontaneously over months to years, often leaving disfiguring, slightly depressed scars.

REPORT OF CASES

Eleven consecutive Israeli patients with a total of 32 lesions of cutaneous leishmaniasis were included in the study. The clinical diagnosis was verified by demonstration of amastigotes in direct smears from the lesions. Leishmania species characterization was carried out by polymerase chain reaction on the stained slides of the direct smears, using primers for the internal transcribed spacer region of the recombinant RNA genes, followed by restriction enzyme digestion with HaeIII. The results were positive for Leishmania in all patients, and restriction digestion of the polymerase chain reaction products gave a pattern typical of L major.

THERAPEUTIC CHALLENGE

Treatment of cutaneous leishmaniasis is directed toward eradication of amastigotes and reduction of the size of the lesions to promote healing with minimal scarring. Therapeutic modalities include systemic treatments such as the use of the pentavalent antimony compounds sodium stibogluconate (Pentostam) and meglumine antimonite (Glucantine), lipid formulations of intravenous amphotericin B, oral ketoconazole or itraconazole, topical paromomycin sulfate, local heat, or freezing with liquid nitrogen. The pentavalent antimony compounds have been in use for more than 50 years, and development of resistance is of increasing concern; they require weeks of intravenous administration and are frequently associated with malaise, anorexia, myalgia and arthralgia, electrocardiographic abnormalities, elevated aminotransferase levels, and chemical pancreatitis. The topical treatments often require multiple repetitions, display modest activity, and are nearly always associated with considerable discomfort because of pain or severe skin irritation.

SOLUTION

Faced with this therapeutic challenge, we tested the effectiveness of photodynamic therapy (PDT) in the treatment of cutaneous leishmaniasis in terms of the number of treatments necessary to obtain eradication of amastigotes from the lesions, reduction of lesion size, cosmetic results, and adverse effects. Ten percent 5-aminolevulinic acid (ALA) in a water-in-oil emulsion was applied locally under occlusion for 4 hours, after which ALA selectively accumulated in the leishmaniasis lesions as demonstrated by fluorescence of ALA-induced porphyrins after exposure to Wood light (Figure, A and B). Irradiation was performed using broadband (570-670 nm) red light (CureLight Broadband; PhotoCure ASA, Oslo, Norway), delivering 100 J/cm² per treatment session at a light intensity of 150 mW/cm². Treatments were repeated at weekly intervals until amastigotes were no longer detectable in direct smears from the lesions. Three to 6 months after the last treatment, the patients were reexamined by means of direct smears and clinical evaluation of the lesions.

All lesions but one were amastigote negative, with a median reduction of 67% in size (P<.005, Wilcoxon signed rank test) after 1 or 2 PDT treatments (Table), and all lesions flattened considerably. Healing was excellent, and most lesions left only superficial scarring or slight postinflammatory hyperpigmentation (Figure, C and D). There was no recurrence of amastigotes during the observation period. Except for a transient burn-
ing sensation in some of the patients, the treatment was without adverse effects and was well tolerated. The single nonresponsive lesion (patient 5) was ulcerated and did not accumulate ALA at the necrotic center. Although the lesion exhibited considerable reduction in size, the direct smears did not become amastigote negative, and the patient was unavailable for follow-up after the third treatment.

**COMMENT**

We report on the effectiveness of PDT in the treatment of cutaneous leishmaniasis caused by *L major* in terms of (1) the number of treatments necessary to obtain eradication of amastigotes from the lesions, (2) lesion size, (3) cosmetic results, and (4) adverse effects. Healing of the cutaneous leishmaniasis lesion involves eradication of lesional amastigotes; tissue remodeling, including flattening of the lesional borders and filling of the ulcerated center; reepithelialization; and reduction of tissue inflammation and postinflammatory hyperpigmentation. Parameters of wound healing include the area and depth of the wound, total time to heal, and rate of healing. These parameters are often difficult to evaluate objectively; therefore, we chose the eradication of amastigotes as our main biological end point for determining the duration of treatment.

Photodynamic therapy involves the administration of a photosensitizing compound and the selective accumulation of the sensitizer molecule in the target lesion, followed by irradiation of the lesion with visible light. In dermatologic settings, topical formulations of ALA are the most commonly used photosensitizers. Exogenous administration of ALA bypasses the rate-limiting enzyme of heme synthesis, ALA synthase, and leads to endogenous buildup of the highly potent photosensitizer protoporphyrin IX. The mechanism of preferential intralesional uptake of precursors and photosensitizers is not fully understood. Interaction of the photosensitizing compound with light of an appropriate wavelength causes destruction of tissue by generation of reactive oxygen species and consequent peroxidation of lipids and crosslinking of proteins, which lead to severe interference with normal cellular functions.

Dermatologic applications of PDT with ALA (ALA-PDT) include cutaneous precancers and malignant neoplasms such as actinic keratoses, basal cell carcinomas, Bowen disease, squamous cell carcinomas, Kaposi sarcomas, and mycosis fungoides. Recently, interest has centered around the antimicrobial activities of PDT. *Propionibacterium acnes* produces porphyrins that absorb light in the near-UV- and blue-light spectrum, and exogenous ALA that accumulates in the pilosebaceous units has been used successfully in the treatment of acne vulgaris. Antiviral activity of ALA-PDT against human papillomavirus was recently demonstrated in a randomized double-blind trial of ALA-PDT for the treatment of recalcitrant foot and hand warts, and photoactivation of toluidine blue has been shown to cause intracellular...
damage in yeast cells. The use of porphyrins in combination with the quinonoid compound menadione causes selective destruction of intracellular Leishmania parasites in vitro, a process that can be explained by autooxidation, which causes the production of superoxide anion radicals and hydrogen peroxide, which, in turn, may mediate cellular damage by lipid peroxidation and inactivation of parasite enzymes.

Certain Leishmania species, such as Leishmania donovani, which lack catalase and glutathione peroxidase activity, are particularly susceptible to oxidative damage. The present report represents the first clinical demonstration of photodynamic action on cutaneous parasitic infections. Photodynamic therapy is an attractive antiparasitic therapeutic modality that offers rapid localized destruction of the diseased lesion without affecting adjacent normal tissue. Furthermore, development of resistance appears unlikely, because selective microbial destruction is mediated by oxidative damage. Although Old World cutaneous leishmaniasis is a potentially self-healing disorder, the rapid eradication of amastigotes and the significant reduction of lesion size only 1 week after treatment are indicative of the effectiveness of PDT. However, the ultimate place of PDT among the various treatment modalities of cutaneous leishmaniasis should be tested in a controlled randomized trial.

Accepted for publication March 17, 2002.

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