Successful Treatment of Cutaneous Sarcoidosis Using Topical Photodynamic Therapy

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

A 67-year-old woman had a 17-year history of increasing numbers of asymptomatic but disfiguring red-brown, flat papules on the extremities. She was otherwise well and had no pulmonary or systemic symptoms. Seven years ago, the patient was referred to our department, and the diagnosis of cutaneous sarcoidosis (small nodular type) was repeatedly confirmed by skin biopsy results.

The physical examination revealed numerous painless, red-brown, slightly elevated papules and plaques up to 1 cm in diameter, disseminated and partially confluent at the extensor aspects of the legs and to a lesser extent on the upper arms. On results of dermoscopy, the lesions appeared gray yellowish. Other body areas were not affected.

Results of the histological evaluation of formalin-fixed, paraffin-embedded biopsy specimens repeatedly obtained from the lesional skin revealed noncaseous epithelioid-cell granulomas with several multinucleated foreign body giant cells and a sparse perifocal lymphohistiocytic infiltrate in the dermis. Results of examination of sections stained with periodic acid–Schiff and Ziehl-Neelsen failed to detect fungi or acid-fast bacilli, respectively. Special cultures repeatedly yielded negative findings for mycobacteria.

Results of internal examinations showed no lung involvement, and pulmonary function test findings were normal. Findings on chest x-ray examination, electrocardiography, abdominal ultrasonography, and neurologic and ophthalmologic examinations revealed no abnormalities. No enlarged peripheral lymph nodes or parotid glands were seen.

Laboratory investigations, including complete blood count, liver and renal function tests, serum electrophoresis, and measurement of electrolyte (including calcium), angiotensin-converting enzyme, β2-microglobulin, and γ-globulin concentrations, were within reference limits. The erythrocyte sedimentation rate and antinuclear antibody concentration were slightly raised. Results of the tine tuberculin reaction test were positive (×3), whereas acute tuberculous and former bacille Calmette-Guérin vaccination were excluded.

Since the diagnosis was made, several treatments had been tried without success. Repeated cryotherapy, topical application of vitamin E, and intralesional and topical corticosteroids did not result in clinical improvement. Oral therapy with clofazimine at a starting dosage of 200 mg/d, followed by 100 mg 3 times weekly for more than 3 months, and a subsequent 1-year course of allopurinol, 300 mg/d, were ineffective. A 1-year course of methylprednisolone-21-hydrogensuccinate with a starting dosage of 40 mg/d, and slow reduction to 8 mg/d yielded improvement, followed by rapid recurrence after discontinuation of the therapy. Therapy consisting of an 8-methoxypsoralen bath combined with UVA light was performed 4 times weekly for 2 months (number of treatments, 20; cumulative light dose, 27.3 J/cm²). Because the lesions did not improve even slightly, the patient did not want to continue this therapy.

In our experience, topical photodynamic therapy (PDT) using 5-aminolevulinic acid (ALA) has shown good results in the treatment of various recalcitrant inflammatory skin disorders in which UV therapy had failed (eg, chronic plaque-type psoriasis, localized scleroderma, or chronic palmoplantar eczema). Because of the failure of the previous therapeutic approaches in our patient with cutaneous sarcoidosis, a therapeutic trial with topical ALA-PDT was started after obtaining written informed consent. We applied 3% ALA in a gel containing 40% dimethyl sulfoxide to the lesions on the patient’s arms and legs and covered these with an occlusive plaster impervious to light. Six hours later, the lesions underwent irradiation by means of an incoherent light source (PDT 1200; Waldmann Medizintechnik, VS-Schwenningen, Germany) emitting light at
a wavelength of 580 to 740 nm (light intensity, 40 mW/cm²; energy density, 20 J/cm²). Photodynamic therapy was performed twice weekly for the first 8 weeks, followed by treatments once a week.

A total of 22 treatments were performed within 3 months. The only adverse effects were a slight burning sensation during irradiation, followed by erythema and edema of the treated area, which lasted for about 2 days after PDT (Figure 2). Roughly 4 weeks after the onset of therapy, the plaques flattened and faded. After 3 months, the skin lesions resolved completely without the development of new lesions. Slight hyperpigmentation of the treated area occurred after 2 weeks of treatment and persisted for about 3 months after the end of PDT (Figure 3). Results of examination of a biopsy specimen obtained from a former lesional site 4 months after therapy also showed histologically normal skin. At the last visit, 18 months after PDT, the patient was still free of skin disease and visceral involvement.

Sarcoidosis is a multiorgan systemic disease that is characterized by the formation of noncaseous epithelioid-cell granulomas in all or several organs. The lung is by far the most commonly involved organ in more than 90% of all cases. In contrast, skin involvement occurs in only about 25% of cases but may be the only manifestation of the disease. The cause of sarcoidosis remains unclear, although infectious causes such as mycobacteria or viruses and genetic factors have been considered. Several therapeutic approaches have been reported for cutaneous sarcoidosis, including topical and systemic corticosteroids, cryotherapy, and immunosuppressive and antimalarial drugs. Some case reports have proposed alternative treatments, such as oral isotretinoin, thalidomide, allopurinol, tranilast, psoralen–UV-A, or photopheresis using hydrocortisone. However, no consistently effective treatment for sarcoidosis exists.
The US Food and Drug Administration approved ALA, a precursor of endogenous porphyrins in the biosynthetic pathway of heme, in December 1999 for PDT for actinic keratoses. After topical application, ALA induces the biosynthesis of photosensitizing concentrations of protoporphyrin IX within rapidly proliferating cells. Subsequent exposure to photoactivating light induces the generation of reactive oxygen species, particularly singlet oxygen. Depending on the light dose applied, cytotoxic effects resulting in tumor destruction and immunomodulatory effects resulting in improvement of inflammatory skin diseases occur. Until now, topical ALA-PDT has been successfully used for the management of superficial skin tumors such as basal cell carcinoma, Bowen’s disease, and actinic keratoses. Inflammatory diseases of the skin, such as psoriasis and localized scleroderma, and human papillomavirus–induced dermatoses, including condyloma acuminatum, epidermodyplasia verruciformis, and verruca vulgaris, respond positively to ALA-PDT. However, to our knowledge PDT has not been described for the treatment of granulomatous skin disorders affecting the dermis.

The formation of granuloma in sarcoidosis occurs in the following 3 steps. First, an immune reaction and T-cell activation occurs. Second, preinflammatory interactions between lymphocytes and macrophages occur, involving tumor necrosis factor α, interleukin 1, and interferon-γ. Third, granuloma formation follows a repair phase when chronic inflammation progresses, resulting in the promotion of fibrosis. In general, a functional predominance of Tₗ1 cells can be demonstrated in sarcoidosis, although the capacity for producing Tₗ2 cytokines seems to be maintained.

Interleukin 1 is important for induction of granuloma formation, whereas tumor necrosis factor α may sustain the inflammatory process. This supposition is supported by a rapid regression of fully developed immune granulomas on tumor necrosis factor α depletion. The release of transforming growth factor β results in a decrease of interleukin 2 production, yielding the cessation of inflammatory processes in sarcoidosis.

Topically applied ALA is primarily taken up by epidermal keratinocytes. On irradiation with red light, cytokines might be released, resulting in a change of the cytokine environment and finally leading to a disruption of the granuloma formation process. However, the exact mechanism by which ALA-PDT exerts its anti-inflammatory effect in sarcoidosis remains to be elucidated.

In our patient, repeated application of topical ALA-PDT resulted in a complete resolution of the skin lesions that had been persistent for more than 17 years and had not responded to conventional and alternative treatments.

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