Topical Sodium Thiosulfate Therapy for Leg Ulcers With Dystrophic Calcification

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 41-year-old African American woman with a 14-year history of systemic lupus erythematosus (SLE) presented with exquisitely painful stellate ulcers with surrounding livedo reticularis on both shins in April 2006. In addition to small-vessel involvement, her connective tissue disease was characterized by pulmonary fibrosis, pulmonary hypertension requiring continuous oxygen supplementation, Raynaud phenomenon, and chronic right popliteal deep venous thrombosis. Her medications included prednisone (5 mg/d), methotrexate (12.5 mg/wk), folic acid, hydroxychloroquine, pentoxyphilline, coumadin, budesonide inhaler, fluticasone inhaler, fexofenadine, erythropoietin, sildenafil, amlodipine, gabapentin, acetaminophen-codeine, tramadol hydrochloride, famciclovir, tolterodine, calcium supplement, vitamin E supplement, alendronate, and esomeprazole. The results of laboratory tests were remarkable for the following values: hemoglobin, 8.8 g/dL (to convert to grams per liter, multiply by 10.0); hematocrit, 27.1% (reference range, 34%-45%); antinuclear antibody, 1:1280 speckled; double-stranded DNA, 52.1 IU/mL (reference value, <5 IU/mL); nRNP/Sm IgG autoantibodies, 118.0 U (<5.0 U); Sm IgG autoantibodies, 114.0 U (reference value, <5.0 U); SSA IgG autoantibodies, 158.0 U (reference value, <5.0 U); SSB IgG autoantibodies, 167.0 U (reference value, <5.0 U); C3 complement, 49 mg/dL (reference range, 82-235 mg/dL), anticardiolipin antibody IgG, 50 IgG phospholipid units (reference value, <15 IgG phospholipid units); and iron, 13 µg/dL (to convert to micromoles per liter, multiply by 0.179) (reference range, 40-170 µg/dL). The findings of urinalysis were normal, as were renal and liver functions. Magnetic resonance imaging of the bilateral lower extremities showed no evidence of osteomyelitis. On examination, the distal portion of the patient's extremities were cyanotic and cold, with sclerodactyly, finger pad atrophy, and bone resorption. The shin ulcers were 10.0×12.5 cm bilaterally.

Initial management included increasing the patient's immunosuppressive regimen with intravenous solumedrol (3 boluses, 1 g each), raising her dose of erythropoietin, and adding oral iron supplements. Intensive topical therapy with daily aluminum subacetate compresses was initiated, followed by the application of hydrogel (polyethylene oxide with 96% water) dressings for pain relief and triamcinolone acetonide, 0.1%, ointment around the wounds. Within 2 weeks, the wound odor had increased. The compress solution was changed to acetic acid for gram-negative bacterial coverage, and the dressing was changed to a hydrophilic polyurethane membrane matrix (foam) dressing.

By late September 2006, the patient's pain was still incapacitating, and her ulcers had increased in size despite the early appearance of deep granulation tissue. Each ulcer was purulent and foul smelling, despite intermittent use of oral ciprofloxacin and clindamycin. There were many small, hard, yellow granules across the surfaces and penetrating the tissue of the wounds (**Figure 1**). Several attempts at debridement were made, but they were extremely painful, requiring preprocedure narcotic administration. Histologic examination of the tissue fragments revealed an ulcerated epidermis with dense neutrophilic infiltration and dermal and subcutaneous suppurative and granulomatous inflammation, with calcification, bone formation, a mixed inflammatory infiltrate, and an area of dermal necrosis (**Figure 2**). A diagnosis of dystrophic calcification in the presence of SLE was made.

THERAPEUTIC CHALLENGE

The challenge was to dissolve the calcium in the patient's chronic leg ulcers in order to promote wound healing, because the calcium deposits were impairing normal regrowth of epithelial tissue across the open wounds.

SOLUTION

At the end of October 2006, a different topical treatment was chosen to target the dystrophic calcium located in the wounds. Twice-weekly in-office applications of 10% sodium thiosulfate solution compresses were begun, followed by the placement of hydrophilic polyurethane membrane matrix dressings on the wounds and topical applications of steroid ointment around the wounds. At home, after normal saline irrigation to prevent the interaction of the 2 solutions, the patient continued daily acetic acid compresses and the dressing applications. Her oral regimen was unchanged, except for the intermittent addition of oral ciprofloxacin and clin-

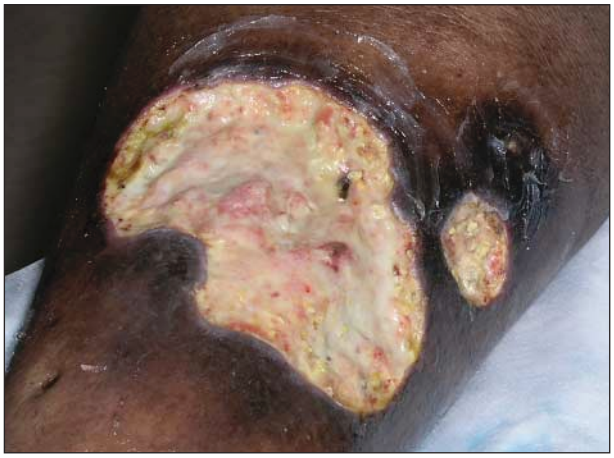

Figure 1. Yellow granules of calcification are seen in the ulcers (October 2006).

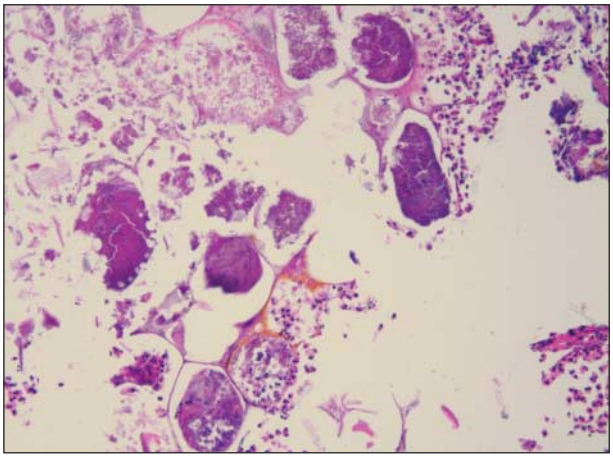

Figure 2. Calcification and abscess formation are seen in the granulating wound base (October 2006).

damycin. The ulcers decreased in size, and clean superficial granulation tissue with healthy-appearing ingrown borders developed. Six months later, the patient had stopped taking clindamycin and the superficial calcium granules had completely dissolved. By July 2007, ciprofloxacin therapy had been discontinued and the ulcers were almost completely epithelialized (**Figure 3**).

Figure 3. Epithelialization is almost complete (August 2007).

COMMENT

Calcinosis cutis, which refers to the deposition of calcium salts in the skin and subcutaneous tissue, is a complication of several connective tissue diseases, including scleroderma, CREST syndrome, mixed connective tissue disease, and dermatomyositis, but it also may rarely be seen in SLE.[1] The disease is typically limited to the extremities and buttocks in patients with long-standing, severe SLE.[2] Calcification is thought to result either from elevated alkaline phosphatase activity, which causes hydrolysis of extracellular pyrophosphatases that normally inhibit calcium deposition, or from phosphate binding to denatured proteins at sites of trauma or inflammation.[3] Other theories of pathogenesis involve the mitochondrial calcium phosphate concentrations and matrix vesicles that may stimulate calcification of proteins.[2,3] Spontaneous resolution of cutaneous calcification is rare; therefore, various therapies have been attempted, including warfarin, colchicine, biphosphonates, calcium channel blockers, minocycline, salicylates, intralesional steroids, oral aluminum hydroxide, and carbon dioxide laser. Each therapy has shown only limited effectiveness, and many have significant adverse effects; no agent has demonstrated clear superiority.[4] In 1 patient with chronic leg ulcers, SLE, and calcinosis cutis universalis, 3 months of oral diltiazem therapy (240 mg/d) was unhelpful.[1] Excision of symptomatic large masses of calcification along with ongoing medical regimens may be useful.[2,3] Indications for surgery include pain, infection, ulceration, physical impairment, and cosmesis.

Soft-tissue calcification has been classified as dystrophic (as in the present case), metastatic, tumoral, idiopathic, and calciphylactic.[4] Dystrophic calcification, which is often seen in dermatomyositis and scleroderma, occurs with normal calcium and phosphorus levels and does not involve the viscera. In contrast, metastatic calcification involves high calcium and/or phosphate levels, which increase the calcium-phosphate product, causing precipitation of calcium salts in tissues. Calciphylaxis (also called calcific uremic arteriolopathy) occurs as a hypersensitivity-type reaction beginning with livedo reticularis and is commonly seen in patients who are undergoing renal dialysis. It consists of calcifications in the media of small to medium-size blood vessels in both the dermis and the subcutaneous tissues. It often manifests with skin necrosis.[5]

Intravenous sodium thiosulfate has been used successfully to treat calciphylaxis and tumoral calcinosis in patients who are undergoing renal dialysis.[6-10] The treatment is generally considered to be safe,[11] with minimal adverse effects other than occasional nausea. Reported acid-base disturbance creating an anion-gap metabolic acidosis appears to be without clinical implication. The mechanism of action involves chelation of calcium into calcium thiosulfate salts, which are much more soluble (250- to 100 000-fold) than other salts of calcium. This process triggers dissolution of the calcium deposits and inhibits further precipitation. Topical sodium thiosulfate is an old and safe treatment for tinea versicolor.[12] We hypothesized that the application of sodium thiosulfate directly on the calcium deposits in our patient's wounds would similarly result in dissolution, leading to pain reduction and healing of the ulcers. The 10% solution was chosen arbitrarily after discussion with the pharmacy department.

In summary, based on previous success using intravenous sodium thiosulfate for the treatment of calciphylaxis, we have found the application of topical 10% sodium thiosulfate solution to be a safe and effective treatment for dystrophic calcinosis cutis. In our patient, the calcification was manifested in ulcers on both shins, and dissolution of the calcium salts led to substantially improved wound healing and markedly decreased pain. We believe this therapy to be a novel and promising method for the treatment of cutaneous calcification, which occurs in many connective tissue diseases.

Accepted for Publication: December 28, 2007.
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Author Contributions: Dr Laumann 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:* Laumann. *Acquisition of data:* Wolf and Laumann. *Analysis and interpretation of data:* Wolf, Smidt, and Laumann. *Drafting of the manuscript:* Wolf, Smidt, and Laumann. *Critical revision of the manuscript for important intellectual content:* Smidt and Laumann. *Administrative, technical, and material support:* Smidt and Laumann. *Study supervision:* Laumann.
Financial Disclosure: None reported.

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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).