Treatment of Recalcitrant Generalized Morphea With Infliximab

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 66-year-old white woman with a history of hypertension and degenerative arthritis was seen in July 2003 by her primary care physician (PCP) for erythematous and sclerotic patches on her trunk. A skin biopsy specimen taken by the PCP at that time was interpreted (by an outside pathology laboratory) to indicate granuloma annulare. The patient began treatment with systemic corticosteroids and ceased taking her antihypertensive medication. However, her cutaneous symptoms continued to progress, and she was referred to our clinic in January 2004.

At that time, the patient denied any illnesses prior to her skin eruption and noted that the only change in her medications was from lisinopril to valsartan. A review of systems found no shortness of breath, dysphagia, worsening of chronic joint symptoms, or Raynaud phenomenon. The patient was noted to have extensive white sclerotic patches and a few eczematous inflammatory patches on the upper chest, breasts (excluding the areola), upper abdomen, flanks, and proximal extremities (Figure 1). Her skin was firm and sclerotic on palpation. No sclerodactyly was present.

A skin biopsy specimen was obtained. Light microscopic examination revealed a striking pandermal sclerosing reaction. The collagen bundles were of wider caliber and oriented parallel to the long axis of the epidermis. In addition, the overlying epidermis was attenuated with prominent hyperkeratosis. The subjacent papillary dermis had a hyalinized appearance with vascular dropout. The findings were compatible with an overlap between morphea and lichen sclerosus et atrophicus (LS&A). In situ hybridization studies demonstrated focal staining of the endothelium for cytomegalovirus (CMV) and tumor necrosis factor (TNF) RNA transcript expression. Direct immunofluorescence showed deposits of C5b-9 within the microvasculature most compatible with a humorally mediated microangiopathy syndrome (Figure 2).

Serologic studies revealed positive anti-CMV IgM and IgG. However, the findings of antinuclear antibody as-

Figure 1. Eczematous inflammatory patches.

says, extractable nuclear protein antibody tests, an interstitial lung battery, complete blood cell count, and comprehensive chemical analysis were all within normal limits, as was the erythrocyte sedimentation rate. The patient was also found to be very hypertensive and resumed taking antihypertensive medications along with class 1 topical corticosteroids.
Standard treatment for generalized morphea (GM) has included topical corticosteroids and lubrication, oral calcitriol, bath PUVA (psoralen–UV-A), UV-A1, intralesional injections of triamcinolone acetonide, and immunosuppressive agents including oral corticosteroids, hydroxychloroquine, methotrexate, sulfasalazine, D-penicillamine, cyclosporine, and cyclophosphamide.1

Once the biopsy results revealed the diagnosis of morphea/LS&A overlap, the patient was started on treatment with escalating doses of oral methotrexate and minocycline and continued treatment with class 1 topical corticosteroids, hydroxychloroquine, methotrexate, sulfasalazine, D-penicillamine, cyclosporine, and cyclophosphamide.1

For our patient, TNF therapy was considered in light of the demonstration of TNF within the vascular endothelium of her biopsy specimen. After her tuberculosis treatment was completed, we initiated infliximab therapy at 5 mg/kg monthly. The patient reported a halt in the progression of her skin lesions along with a decrease in skin tightness after the second infusion of infliximab. Physical examination revealed a decrease in sclerosis and dyschromia of her skin lesions. A biopsy specimen taken after 4 monthly infusions of infliximab demonstrated a residual sclerodermoid reaction with significant reduction in fibroplasia compared with specimens taken prior to infliximab treatment. The sclerosis was much improved: the extent and depth were lessened; the collagen bundles were of thinner caliber; and TNF expression was essentially negative (Figure 3). After 4 monthly infusions of infliximab, findings of our patient’s physical examination demonstrated a significant reduction in clinical sclerosis and dyschromia on the trunk and extremities (Figure 4).

Generalized morphea is one of the most severe subtypes of localized scleroderma. Characterized by widespread
skin involvement and sometimes muscle involvement. GM is distinguished from systemic scleroderma because it lacks symptoms of Raynaud disease, sclerodactyly, and internal organ involvement. It occurs most frequently in white women and presents with multiple indurated plaques with variable dyschromia. These plaques may result in severe scarring and joint disability. Antinuclear antibody, antihistone antibody, single-stranded DNA antibody, and/or rheumatoid factor findings might be positive in patients with GM. Furthermore, several studies have documented increased levels of cytokines and growth factors, including TNF, which has several inflammatory properties including an influence on fibroblast growth and collagen synthesis. The cutaneous fibrosis seen in GM is the result of overproduction and accumulation of collagen and extracellular matrix proteins.

The pathophysiologic basis of scleroderma is very complex and has not been fully elucidated. However, a series of events has been proposed: immune-based endothelial cell injury is followed by ischemia with its inherent effects on the promotion of collagen synthesis. The helper T cell type 2 dominant cytokine milieu associated with the humoral response as well as T cells responding directly to antigenic epitope (ie, topoisomerase) contribute further to fibroblast activation. In addition, a genetic predisposition may lead to an excessive procollagen response. In regard to the humoral limb, the main focus of injury is likely endothelium, given the presence of circulating antienhancedel cell antibodies in patients with scleroderma and the morphologic changes of the affected small vessels. These morphologic changes include those that we traditionally associate with humorally mediated microvascular injury including intraluminal thrombus, endothelial cell necrosis, and basement membrane zone reduplication.

In our patient, the presence of C5b-9 in the blood vessels was corroborative of immune-based microvascular injury. The end sequela of local tissue anoxia is the upregulation of transforming growth factor β (TGF-β), an important promoter of collagen synthesis, a response that is presumably dysregulated in the patient with scleroderma. Indeed, TGF-β receptors are increased in density in scleroderma fibroblasts. Scleroderma fibroblasts produce increased collagen and other extracellular matrix proteins; fibroblasts are the effector cells in this disease.

Our patient had evidence of active CMV infection, and her endothelial cells showed CMV transcript expression. There is a strong link between scleroderma and CMV infection. The basis is likely a combination of molecular mimicry whereby (1) CMV proteins cross-react with those implicated in scleroderma; (2) CMV early proteins alter the cytokine milieu to one that is profibroblastic through the enhancement of TGF-β; and (3) the virus exerts its inherently tropic effects on the endothelium. The tropic effects of the virus lead to accelerated apoptosis via upregulation of the TNF pathway. Not only is enhanced TNF critical in accelerating endothelial cell apoptosis, but it is also known to participate in the various steps that lead to scleroderma, including activation of vascular endothelium, upregulation of adhesion molecules, induction of cellular apoptosis, and modulation of fibroblast function.

Traditional scleroderma treatments including systemic corticosteroids, methotrexate, and cyclosporine are not uniformly effective; in addition, they are associated with substantial adverse effects. Infliximab is currently indicated for the treatment of rheumatoid arthritis, ulcerative colitis, Crohn disease, ankylosing spondylitis, and psoriatic arthritis. Case reports have demonstrated clinical improvement in lung fibrosis and pulmonary hypertension in patients with scleroderma and in skin lesions in a patient with CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) when they were treated with infliximab. Our patient with GM demonstrated remarkable improvement after treatment with infliximab. This agent may serve as an alternative therapeutic approach for patients with similar presentations. However, it is important to note that the natural course of all sclerosing disorders is to “burn out” over time, and so randomized controlled studies are needed. These studies are currently lacking, and all treatments that have appeared to show improvement in sclerosing disorders have failed to do so in the context of controlled studies.

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Author Contributions: Dr Diab 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: Diab and Bechtel. Acquisition of data: Diab, Magro, and Bechtel. Analysis and interpretation of data: Diab, Coloe, Magro, and Bechtel. Drafting of the manuscript: Diab. Critical revision of the manuscript for important intellectual content: Diab, Coloe, Magro, and Bechtel. Administrative, technical, and material support: Coloe. Study supervision: Diab and Bechtel.

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The article by Cordain and colleagues is an observational study that evaluates 2 isolated nonwesternized populations: the Kitavan Islanders of Papua New Guinea and the Ache hunter-gatherers of Paraguay, who have a lack of acne. Dietary limitations are the only control. The glycermic index of their diets is substantially lower than that of a Western diet. Their genetic backgrounds are similar to those of other South American Indians and Pacific Islanders, who live in more westernized settings and have a considerably higher incidence of acne.

These results have helped to spark new interest in the relationship between diet and acne. However, dietary advice has not been incorporated into the mainstream standard of care for the treatment of acne. Certainly, it is not recommended as monotherapy. Until we have prospective, randomized, well-controlled studies, we will not fully understand the efficacy of dietary interventions.

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