Treatment of Multicentric Reticulohistiocytosis With Etanercept

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

An otherwise healthy 46-year-old man presented with a 1-year history of an ill-defined acral eruption that had evolved over several weeks into reddish-brown papules and nodules, together with a progressive inflammatory polyarthritis. Skin lesions ranging from several millimeters to several centimeters in diameter were present on the dorsal and palmar aspects of the hands (Figure 1) and on the forearms, extensor elbows, chest, paranasal face, neck, pinnae, and scalp. A skin biopsy revealed an intradermal infiltrate composed predominantly of histiocytes and multinucleated giant cells. Many of the cells had abundant “ground glass” cytoplasm with fine periodic acid-Schiff–positive granules (Figure 2). There was severe stiffness, pain, and swelling associated with bilateral synovitis of the metacarpophalangeal joints, distal and proximal interphalangeal joints, wrists, elbows, shoulders, knees, ankles, and forefeet.

Laboratory values, including complete blood cell count, general chemistry panel, erythrocyte sedimentation rate, rheumatoid factor, and antinuclear antibodies were within normal limits except for an elevated total cholesterol level of 262 mg/dL (6.80 mmol/L). The test result for perinuclear antineutrophil cytoplasmic antibodies was positive but no titer was reported and antibodies to myeloperoxidase were not obtained. A chest radiograph was unremarkable.

The patient was diagnosed with multicentric reticulohistiocytosis (MRH) and initially managed with 20 mg of methotrexate weekly and 20 to 40 mg of prednisone daily for 2 months. Hydroxychloroquine was added to this regimen for 7 months with little benefit. Subsequent treatment with chlorambucil and prednisone for 3 months was accompanied by a worsening of the skin and joint disease. Radiographs taken 2 years after disease onset revealed erosive articular damage in the hands (Figure 3) and right hip. Combination therapy with cyclophosphamide (up to 200 mg daily), methotrexate (up to 25 mg weekly), and prednisone (20 mg daily) resulted in gradual improvement of only the skin eruption over 8 months, but cyclophosphamide was discontinued after the onset of gross hematuria.

Multicentric reticulohistiocytosis is a potentially disfiguring and crippling disease for which no consensus has been reached regarding treatment. Therapies with corticosteroids, hydroxychloroquine, methotrexate, alkylating agents such as chlorambucil and cyclophosphamide, and azathioprine have been used with mixed
success. The challenge in this case was to determine a safe and effective treatment for both the skin and joint manifestations of the disease.

**SOLUTION**

Immunohistochemical staining of the inflammatory infiltrate in MRH has demonstrated the presence of histiocytes of a monocyte-macrophage origin and an abundance of cytokines, including tumor necrosis factor α (TNF-α). The production of TNF-α and other cytokines by monocytes and macrophages plays a central role in many inflammatory conditions: TNF-α has been found in synovium and synovial fluid from joints of patients with several forms of inflammatory arthritis that may be successfully treated with anti-TNF agents. The predominance of histiocytes in the infiltrate of MRH and the detection of TNF-α inspired a trial of an anti-TNF agent, etanercept, as treatment for our patient.

Biweekly treatment with etanercept, 25 mg by subcutaneous injection, was started in addition to continuing treatment with prednisone, 20 mg daily, and methotrexate, 15 mg weekly. With this regimen there was improvement in skin and joint symptoms within 1 month, and prednisone was tapered over 7 months. The patient experienced a flare of skin lesions and arthritis as the dose of prednisone was reduced to 10 mg daily. At that time, treatment with etanercept, 25 mg biweekly, and prednisone, 10 mg daily, was continued, and methotrexate was replaced with leflunamide, 20 mg daily. Skin lesions and synovitis completely resolved with this regimen, which permitted a decrease of the prednisone dosage to 5 mg daily without a flare of symptoms for 10 months (Figure 4). There was some progression of articular deformities despite the control of synovitis. We believe that this resulted from articular damage that had previously occurred. The dosages of leflunamide and prednisone were recently decreased to 20 mg every other day and 4 mg daily, respectively, and treatment with etanercept was continued. The patient has remained symptom free for 2 months. We plan to continue tapering prednisone and leflunamide dosages if symptoms remain controlled.

A rare multisystem disease of unknown etiology characterized by a histiocytic infiltrate in the dermis and synovium, MRH manifests as a papulonodular eruption and symmetric inflammatory polyarthritis. It tends to have an insidious onset, most commonly in the fourth decade of life, and is slightly predominant in women. At presentation, about 40% of patients have only joint symptoms, 30% only skin symptoms, and 30% both skin and joint symptoms. Active disease often remits after approximately 8 years and, although it is not considered a paraneoplastic syndrome, it occurs with an associated malignancy in about 20% of cases. Other sites of involvement can include the heart, lungs, thyroid, and bone marrow. Constitutional symptoms such as fever, malaise, and weight loss have been described, as have an elevated erythrocyte sedimentation rate, anemia, and hypercholesterolemia. Antibodies to neutrophil cytoplasmic antigens have not been reported in MRH. Antibody specificity was not determined in our patient.

Cutaneous manifestations include pink, red, or brown papules and nodules ranging from 1 millimeter to several centimeters in diameter and occurring most frequently on the dorsal aspect of the hands and on the face. Other sites of involvement include the arms, scalp, pinnae, and neck. Papules often occur in a periungual distribution, producing a characteristic “coral beads” appearance. Mucosal involvement, which includes the tongue and buccal or nasal mucosa, occurs in roughly one third of cases.

A symmetric inflammatory polyarthritis can affect any synovial joint, including the hands, knees, wrists,
shoulders, elbows, ankles, hips, feet, and spine. The arthritis can be rapidly progressive and destructive. Well-circumscribed marginal erosions and juxtarticular reabsorption are typical, often creating the appearance of a widening of the joint space. Severe involvement of the interphalangeal joints may cause shortening and telescoping of the involved fingers, forming characteristic “opera glass hands.” It has been proposed that this joint destruction is mediated by urokinase released by activated histiocytes.

Histologically, MRH can be recognized by a dermal or synovial infiltrate containing histiocytes and multinucleated giant cells with abundant cosinophilic, finely granular, ground-glasslike cytoplasm. The cytoplasm is periodic acid–Schiff positive and diastase resistant. These giant cells may be few in early lesions. In addition to histiocytes, small numbers of lymphocytes may be found in the infiltrate. As mentioned, immunohistochemical staining has revealed the presence of inflammatory cytokines, including TNF-α, interleukin 1β, and interleukin 12.

As in MRH, high levels of TNF-α have been found in the synovium and synovial fluid of joints affected by other inflammatory arthritides such as rheumatoid arthritis, juvenile rheumatoid arthritis, and psoriatic arthritis. All of which have been successfully treated with anti-TNF agents. Mice overexpressing TNF-α also develop joint inflammation. Etanercept is a genetically engineered fusion protein made up of soluble TNF-α receptor fused to the Fc portion of IgG1 that binds circulating TNF-α. The predominance of histiocytes and presence of TNF-α in the inflammatory infiltrate of affected skin and joints make anti–TNF-α agents a logical therapeutic option in MRH. Matejicka et al recently reported a case of MRH in a 22-year-old woman resistant to treatment with prednisone, methotrexate, nonsteroidal anti-inflammatory drugs, hydroxychloroquine, cyclophosphamide, and cyclosporine who responded well to a combination of etanercept, methotrexate, and prednisone. This patient remained symptom free with a regimen of etanercept and hydroxychloroquine. Our experience with etanercept also suggests that anti-TNF agents may have an important role in the treatment of MRH.

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