

# Successful Etanercept Therapy for Refractory Sacroiliitis in a Patient with Ankylosing Spondylitis and Mixed Connective Tissue Disease

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The concurrence of ankylosing spondylitis (AS) in a patient with mixed connective tissue disease (MCTD) is rarely described in the literature. Significant and sustained efficacy with tumor necrosis factor (TNF)- $\alpha$  blockers has been demonstrated in AS patients. However, evidence to date has revealed associated side effects, including antinuclear antibody induction and development of a lupus-like syndrome. Several authors have reported lupus-like manifestations in MCTD patients treated with TNF- $\alpha$  blockers used to control peripheral polyarthritis. In our case report, we demonstrate a good response to etanercept therapy for refractory sacroiliitis in a patient with coexisting AS and MCTD, without development of a lupus-like syndrome. This demonstrates that etanercept therapy may be an appropriate therapeutic agent for sacroiliitis in MCTD patients, as it is in AS alone.

**Key Words:** Ankylosing spondylitis, mixed connective tissue disease, etanercept

## INTRODUCTION

Mixed connective tissue disease (MCTD) was first described as a distinct disease entity characterized by high titers of anti-U1-ribonucleic protein (RNP) antibodies.<sup>1</sup> With certain sets of diagnostic criteria, clinical manifestations of MCTD are similar, or intermingled, with those of other connective tissue diseases, including systemic lupus erythematosus (SLE), polymyositis, and

systemic sclerosis.<sup>2</sup> However, a concurrence of ankylosing spondylitis (AS) and MCTD has rarely been reported, in spite of their being clinically distinct entities.<sup>3,4</sup>

Most MCTD patients with arthritis respond well to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), hydroxychloroquine, and/or an oral, low-dose steroid. TNF- $\alpha$  blockers, including etanercept or infliximab, are also effective in controlling polyarthritis in MCTD patients,<sup>5,6</sup> although side effects of lupus-like manifestations have been described. Treatment with TNF- $\alpha$  blockers in AS has also shown significant clinical efficacy.<sup>7,8</sup> We present a patient with AS sacroiliitis and MCTD who showed good response to etanercept without development of a lupus-like syndrome.

## CASE REPORT

A 45-year-old female presented with Raynaud's phenomenon, photosensitivity, edematous fingers and hands, and polyarthritis in April 2004. She also complained of a three-year history of low back pain with morning stiffness that improved with exercise and worsened with resting.

Physical examination revealed symmetrical edematous fingers and hands bilaterally, with pain and limited motion of the right shoulder. Chest wall expansion was estimated at 3 cm, and lumbar spine motion was approximately 2 cm. Sacroiliac joint tenderness on palpation was noted.

Immunological analyses revealed positive antinuclear antibody (ANA) with specked pattern

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(titer of 1:1280, normal <1:40), and positive anti-RNP antibody (titer of 965, normal <150). Antibodies for double-stranded DNA, Sm, SS-A/Ro, SS-B/La, centromere, Scl-70, and Jo-1 were negative. Anti-neutrophil cytoplasmic antibody, anti-cardiolipin antibody, cryoglobulin, VDRL, and rheumatoid factor were not detected. HLA-B27 antigen was positive.

On radiographic examination of the pelvis, grade 2 bilateral sacroiliitis was diagnosed according to the modified New York classification. However, typical cervical and lumbar spine syndesmophytes were not identified. Magnetic resonance imaging (MRI) revealed active bilateral sacroiliitis (Fig. 1A). Echocardiography identified pulmonary arterial hypertension, with a pulmonary arterial pressure of less than 25 mmHg. Positive Raynaud's phenomenon using Raynaud's scan and infrared thermographic imaging was also confirmed.

AS was diagnosed according to the modified New York criteria,<sup>9</sup> and MCTD was diagnosed by the Alarcon-Segovia's criteria.<sup>10</sup> Polyarthritides symptoms, except low back pain and Raynaud's phenomenon, improved with combination therapy of hydroxychloroquine, NSAIDs, and low-dose corticosteroids, and right shoulder pain resolved following intraarticular steroid injection.

Four months later, the patient was readmitted for buttock and sacroiliac joint pain. Clinically significant pain reduction was not achieved using computed tomography-guided intraarticular injection of 40 mg of triamcinolone acetate. A 25-mg dose of soluble TNF- $\alpha$  receptor, etanercept, was started twice weekly for four weeks in combination with NSAIDs and corticosteroids. The patient had pain reduction and no occurrence of

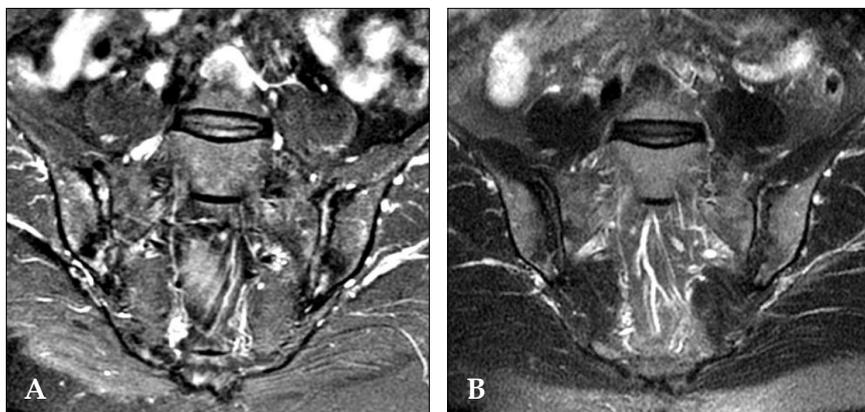
lupus-like symptoms.

MRI examination of the sacroiliac joint was assessed at 18 months. A significant decrease in inflammation was identified, without development of new lesions (Fig. 1B); this suggested the effectiveness of etanercept for sacroiliitis in patients with MCTD. Unfortunately, mild pulmonary arterial hypertension of approximately 37 mmHg developed. The patient's treatment continued with NSAIDs, hydroxychloroquine, low-dose corticosteroid, and a calcium channel blocker. She reported a tolerable level of low back pain around the sacroiliac joints.

## DISCUSSION

MCTD patients share a number of clinical features, including Raynaud's phenomenon, puffy hands, arthralgia, mild arthritis, myositis, and a high level of antibodies to U1-RNP. Several diagnostic criteria for MCTD have been described in patients with overlapping manifestations of SLE, RA, systemic sclerosis, and polymyositis.<sup>2</sup> In addition, evidence of coexistence of spondyloarthropathy and connective tissue diseases, especially Sjögren's syndrome or sicca syndrome, has previously been described.<sup>11,12</sup> Our case was a rare concurrence of AS and MCTD.

Inflammatory manifestations in MCTD (including arthritis, serositis, fever, and skin rash) respond relatively well to NSAIDs or corticosteroids, whereas patients with major organ involvement tend to have persistent symptoms and often fail to have significant improvement of Raynaud's phenomenon, interstitial lung disease, scleroderma-



**Fig. 1.** (A) Magnetic resonance coronal fat suppressed T2-weighted image (WI) of both sacroiliac joints showing increased signal intensity within the joint spaces and subchondral marrow edema. Also present are subchondral erosions and localized fat deposition in the subchondral marrow spaces. (B) After 18 months, significant improvement of joint spaces with high signal intensity on fat-suppressed T2-WI with subchondral marrow edema identified at the same level.

like skin thickening, or pulmonary hypertension.<sup>13</sup> Arthritis in MCTD patients is responsive to NSAIDs, hydroxychloroquine, and/ or low-dose corticosteroids. Our patient with mild and nonerosive polyarthritis had significant improvement following combination therapy. Patients with more destructive and erosive arthritis may require more aggressive therapies, including methotrexate, leflunomide, or azathioprine.<sup>13</sup>

Data on TNF- $\alpha$  blockers efficacy and safety have been recognized for multiple diseases with inflammatory peripheral arthritis or axial arthritis /spondylitis, including RA and AS.<sup>7,8,14</sup> Treatment has been associated with diverse autoimmune toxicities, including anti-double-stranded DNA antibody induction and development of systemic, lupus-like syndromes or a cutaneous, lupus-like rash, although the etiology of aberrant immune responses it is not clearly understood.<sup>15</sup> We proposed that our patient with MCTD and bilateral refractory sacroiliitis unresponsive to NSAIDs and intraarticular steroid injections may do well with TNF- $\alpha$  blocker therapy, as do AS patients. However, two reports previously described development of a lupus-like syndrome in MCTD patients.<sup>5,6</sup> In this case we used etanercept with good result, and without occurrence of clinical features consistent with lupus-like syndrome, such as myalgia, fever, arthralgia, or skin rash.

As our patient had MRI scanning at 18 months, it is impossible to predict time of sacroiliac lesion improvement. However, a German study group found significant regression on MRI of active sacroiliitis following 6 weeks of treatment.<sup>16</sup> For more accurate assessment, periodic MRI examination, development of an MRI scoring system, and standardized dosing and duration of etanercept in a large population study would be required.

We report safe and effective use of etanercept for sacroiliitis in a patient with MCTD with evidence of symptomatic and radiological improvement. The results of these few case reports show that there may be efficacy in the use of anti-TNF therapy in MCTD-related polyarthritis. If used, patients should be warned of the risk of development of a lupus-like syndrome.

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