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Case Report

Infliximab in the Treatment of an HIV Positive Patient with Reiter's Syndrome

NORMAN GAYLIS

ABSTRACT. Reiter's syndrome is an acute inflammatory arthritis with no standard treatment options for patients unresponsive to nonsteroidal antiinflammatory drugs (NSAID). In patients positive for human immunodeficiency virus (HIV), HIV-RNA levels have been correlated with elevated tumor necrosis factor-α (TNF-α) levels. We investigated the safety and activity of infliximab, an anti-TNF-α chimeric monoclonal antibody, in the treatment of an HIV positive patient with Reiter's refractory to NSAID therapy. A 41-year-old HIV positive man with Reiter's syndrome was treated with infliximab 300 mg intravenously at Weeks 0, 2, and 6 and then every 6 to 7 weeks thereafter. He presented with severe fatigue, pain, muscle wasting, synovitis of the elbows, wrists and knees, a scaly rash in the groin area, burning during urination, and severe onycholysis on all digits. Laboratory assessment revealed hemoglobin 7.8 g/dl, erythrocyte sedimentation rate (ESR) 152 mm/h, white blood cell count 5700 cells/mm^3, and C-reactive protein (CRP) 65.7 mg/dl. HIV viral load on presentation was 1600 quantitative:ultrasensitive (Qn:US) copies/ml, decreased from a maximum of 428,000 Qn:US copies/ml at the start of antiretroviral therapy. After 6 months taking infliximab, all complaints resolved, nails regrew, and the rash cleared. CRP decreased to 0.8 mg/dl and ESR to 22 mm/h. During this 6 month period antiretroviral therapy remained unchanged, and the viral titer remained below 400 Qn:US copies/ml. (J Rheumatol 2003;30:407–11)

Key Indexing Terms:
HUMAN IMMUNODEFICIENCY VIRUS REITER'S SYNDROME
MONOCLONAL ANTIBODY CA2

Reiter's syndrome is an acute seronegative spondyloarthropathy associated with inflammatory synovitis, conjunctivitis, urethritis, arthritis, onycholysis, and enthesitis (sausaging of toes or fingers, Achilles tendonitis, and plantar fasciitis). Joint involvement is typically asymmetric and oligoarticular. Mucocutaneous involvement is common, especially keratoderma blennorrhagica, circinate balanitis, and psoriasis. Reiter's syndrome is more common in men and frequently follows an infection with Chlamydia trachomatis[1-3]. Enteric infections with *Shigella, Salmonella,* or *Campylobacter* can also cause Reiter's syndrome[4,5].

Many arthropathies have been associated with human immunodeficiency virus (HIV) infection. In 1987, the first case of HIV associated Reiter's syndrome was described[5]. HIV associated Reiter's syndrome has a clinical presentation similar to that of conventional Reiter's syndrome. Reports on the prevalence of Reiter's syndrome in HIV infected individuals have ranged from 1.7 to 11.2%[6]. Currently, HIV associated Reiter's syndrome is treated with nonsteroidal antiinflammatory drugs (NSAID) followed by methotrexate (MTX), sulfasalazine, hydroxychloroquine, or etretinate. However, many patients are refractory to these therapies.

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine; TNF-α induces the release of interleukin 1 (IL-1) and IL-6 and enhances neutrophil, monocyte, and lymphocyte migration. Evidence supporting the role of TNF-α in autoimmune rheumatic diseases such as rheumatoid arthritis (RA), psoriasis and psoriatic arthritis (PsA), and ankylosing spondylitis continues to accumulate. TNF-α is elevated in the sera and synovial fluid of patients with RA[7,8], and anti-TNF-α antibodies have been shown to inhibit polyarthritic disease in 2 mouse models[9,10]. Circulating T lymphocytes and macrophages isolated from patients with PsA produce increased amounts of TNF-α compared with cells isolated from healthy controls[11], and TNF-α is elevated in the synovial fluid[12,13] and skin lesions[14,15] of patients with PsA. TNF-α is also elevated in the plasma of patients with ankylosing spondylitis and is correlated with disease activity[16]. The role of TNF-α in numerous rheumatic diseases suggests TNF-α may also play a role in other autoimmune diseases such as Reiter's syndrome.

Infliximab, an anti-TNF-α agent, is a chimeric immunoglobulin G1 kappa monoclonal antibody approved for the treatment of active MTX refractory RA and Crohn's disease. Infliximab neutralizes the biologic activity of TNF-α

From the Department of Rheumatology, University of Miami, Miami, Florida, USA.
N. Gaylis, MD.
Address reprint requests to Dr. N. Gaylis, Arthritis and Rheumatic Disease Specialties, 2845 Aventura Blvd., Suite 100, Aventura, FL 33180. E-mail: ngaylis@aol.com
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by binding to and inhibiting the binding of this cytokine to its receptors[17-19].

CASE REPORT

In April 2000, a 41-year-old, gaunt Hispanic man weighing 72.57 kg with a 6 year history of HIV infection secondary to heterosexual contact presented with severe distress and complained of severe fatigue, wasting, and severe pain of 4 months' duration in his back, knees, shoulders, elbows, fingers, and toes. He had an intravenous (IV) portal through which he was receiving antibiotic therapy for a presumptive diagnosis of osteomyelitis of his right toe. Biopsies and cultures subsequently performed to confirm osteomyelitis were negative. He had received numerous antibiotics, including vancomycin, which caused renal insufficiency. A turbid aspirate with increased white blood cells (WBC) was obtained from his right knee, but was negative to culture.

Radiographs of the right knee were unremarkable. He was unable to transfer or raise his arms above his shoulders and used a walker for ambulation. Synovitis of elbows, wrists, distal interphalangeal joints, knees, ankles, and metatarsal joints was present. Swelling and erythema were observed in several joints, particularly in the fingers and toes, associated with diffuse, symmetrical pain. Limited extension of both elbows and marked limitation of lumbar extension and restricted cervical movement were noted. He could not straighten his lumbar spine and had marked pain over both sacroiliac joints. He had severe onycholysis of all fingernails and toenails (Figure 1). A scaly rash was present in his groin bilaterally and around the head of the penis, and he experienced burning on urination. Radiographs of his back and feet revealed no sacroiliac involvement. There was some mild osteopenia of the distal staff tuft of the right great toe.

The treatment history included multiple NSAID and antibiotics to treat his inflammatory arthritis and the presumptive diagnosis of osteomyelitis. He had started antiretroviral therapy (ritonavir 400 mg twice a day, lamivudine 150 mg/day, zidovudine 300 mg/day, and saquinavir mesylate 400 mg twice a day) in January 2000, with his HIV viral load being as high as 427,597 quantitative:ultrasensitive (Qn:US) copies/ml. It appeared that the musculoskeletal and rash symptoms emerged when his HIV titer was at this level. On presentation, his HIV viral load had been reduced to 1600 Qn:US copies/ml. He tested negative for rheumatoid factors and antinuclear antibodies. Initial laboratory findings included hemoglobin (Hb) 7.8 g/dl, erythrocyte sedimentation rate (ESR) 152 mm/h, red blood cell (RBC) count 2.3×10^6 cells/µl, hematocrit 23.2%, WBC count 5700 cells/mm^3, and C-reactive protein (CRP) 65.7 mg/dl. His absolute CD4+ count at base-

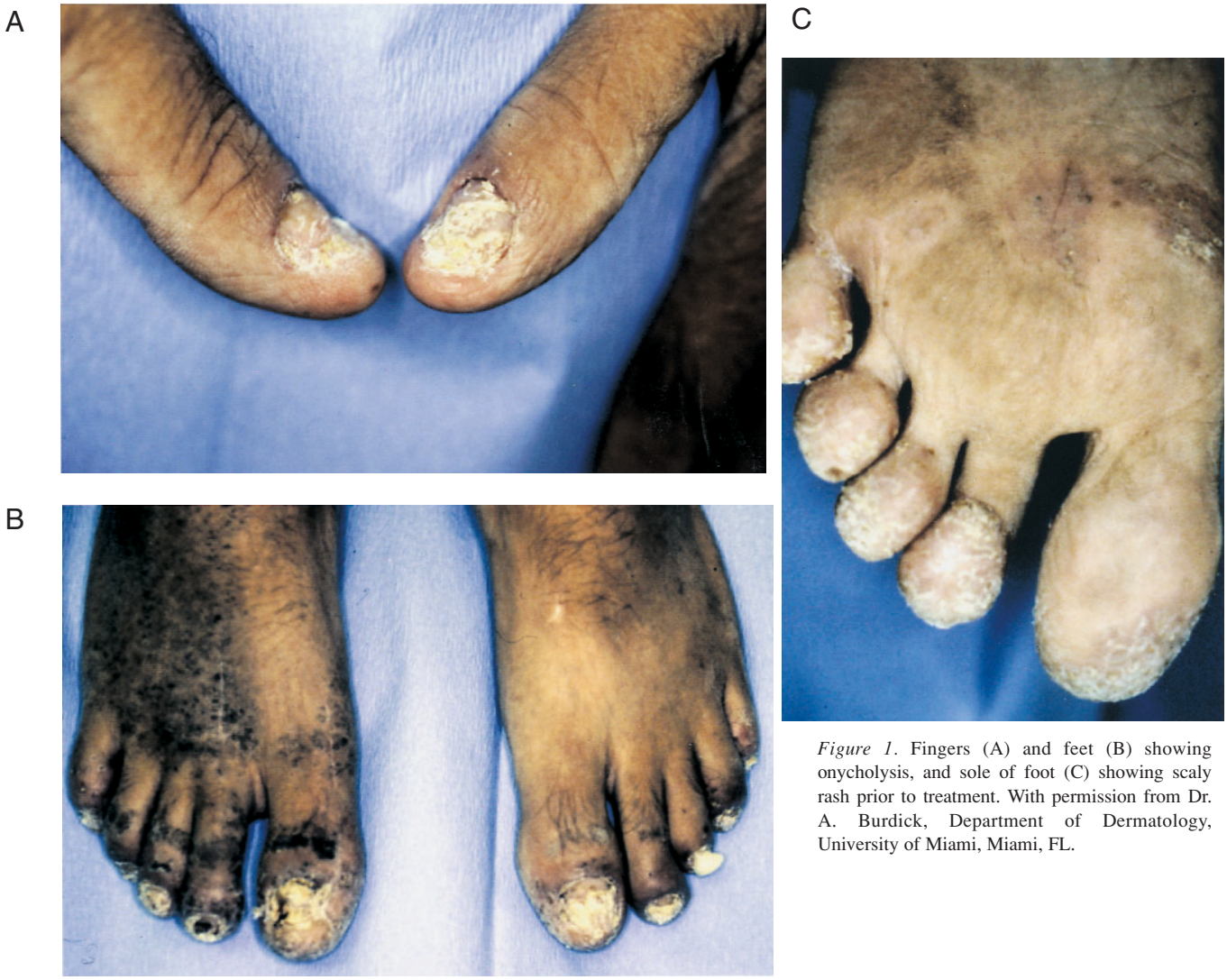

Figure 1. Fingers (A) and feet (B) showing onycholysis, and sole of foot (C) showing scaly rash prior to treatment. With permission from Dr. A. Burdick, Department of Dermatology, University of Miami, Miami, FL.

line for therapy was 27.5 cells/mm^3. Tests for human leukocyte antigen B27 and hepatitis B surface antigen were negative. He was anergic to a tuberculosis skin test.

The clinical diagnosis was HIV associated Reiter's syndrome. He was given a combination of IV MTX 20 mg/wk, oral prednisone 20 mg/day, and a pulse treatment of IV methylprednisolone 1 g. He initially responded well to this combination therapy; joint pain, rash, and nail abnormalities were reduced and he experienced increased range of motion. Over the next month Hb increased to 9.8 g/dl and ESR decreased to 5 mm/h. However, by the beginning of July 2000, after almost 3 months of MTX treatment, his condition was declining. Symptoms recurred, including rashes, joint pain of the hands, feet and sacroiliac joint, and breakdown of nail beds, despite weekly MTX, daily prednisone, and 2 further pulse treatments of methylprednisolone 1 g. His ESR increased to 93 mm/h and his absolute CD4+ count was 770 cells/mm^3.

In August 2000, his disease was no longer responsive to corticosteroid and MTX therapy, and infliximab was added to the treatment regimen. Infliximab was initiated at a dose of 300 mg, roughly 3 mg/kg body weight. At the onset of infliximab treatment his viral titer was < 500 Qn:US copies/ml. He was given 2 additional 300 mg doses of IV infliximab at Weeks 2 and 6 and then received single 300 mg IV infliximab doses every 6 to 7 weeks. In November 2000, his laboratory findings were Hb 14.2 g/dl, ESR 112 mm/h, RBC 3.78 × 10^6 cells/µl, hematocrit 39.5%, WBC 5200 cells/mm^3, and CRP 14.6 mg/dl. His absolute CD4+ count was 693 cells/mm^3. During this treatment regimen he experienced complete resolution of all symptoms. The rash and joint swelling resolved and nails regrew (Figure 2).

With infliximab therapy the patient was functional, had no pain, had full range of movement, and was able to discontinue corticosteroid use. Shortly before each infliximab course, he reported an increase in back pain and arthralgias. Therefore, he continued a regimen of intramuscular MTX 15 mg/wk and IV infliximab 300 mg every 6 to 7 weeks, and by February 2001 his CRP had decreased to 0.8 mg/dl and ESR to 22 mm/h. His blood chemistry profile was normal and he weighed 82.55 kg. Through February 2001, his antiretroviral therapy remained unchanged and his viral titer remained below 400 Qn:US copies/ml. Improvements in CRP, ESR, and blood chemistry profile were maintained through June 2001. His CD4+ count remained in the normal range with a count of 814 cells/mm^3. Infliximab was well tolerated, with no adverse events reported over 18 months of therapy.

DISCUSSION

The current initial treatment for HIV associated Reiter's syndrome is NSAID therapy. However, there are no standard treatment regimens for patients with Reiter's who do not respond. Patients who have an inadequate response to treatment with NSAID are treated with MTX, sulfasalazine, hydroxychloroquine, or etretinate[20-26]. However, sulfasalazine is often ineffective against the skin manifestations of Reiter's syndrome, and MTX has been associated with myelosuppression and the development of potentially fatal opportunistic infections in HIV infected patients[5,27]. In addition, HIV associated Reiter's syndrome can become resistant to conventional therapies, and patients often fail to achieve or maintain an adequate response. Other therapeutics for the treatment of Reiter's syndrome in HIV positive patients are therefore needed.

Anti-TNF-α therapy is effective in the treatment of RA, and recent reports suggest it is also effective in other rheumatic disorders. Infliximab, an anti-TNF-α agent, has been effective in halting both joint space narrowing and joint erosion in patients with RA refractory to MTX treatment alone[28,29]. Recently, infliximab has also been reported to be effective in the treatment of PsA[30,31] and ankylosing spondylitis[32,33]. The successful treatment of patients with RA, PsA, and ankylosing spondylitis suggests that anti-TNF-α therapy may also be effective in the treatment of other autoimmune disorders including Reiter's syndrome.

Elevated TNF-α levels have been associated with HIV infection[34]. Further, TNF-α stimulates HIV replication and has been correlated with HIV viral load[34-36]. Thalidomide, an inhibitor of TNF-α mRNA[37] and TNF-α protein production[38], has been shown to reduce wasting in patients with HIV[34]. Etanercept, a soluble TNF receptor (p75):Fc fusion

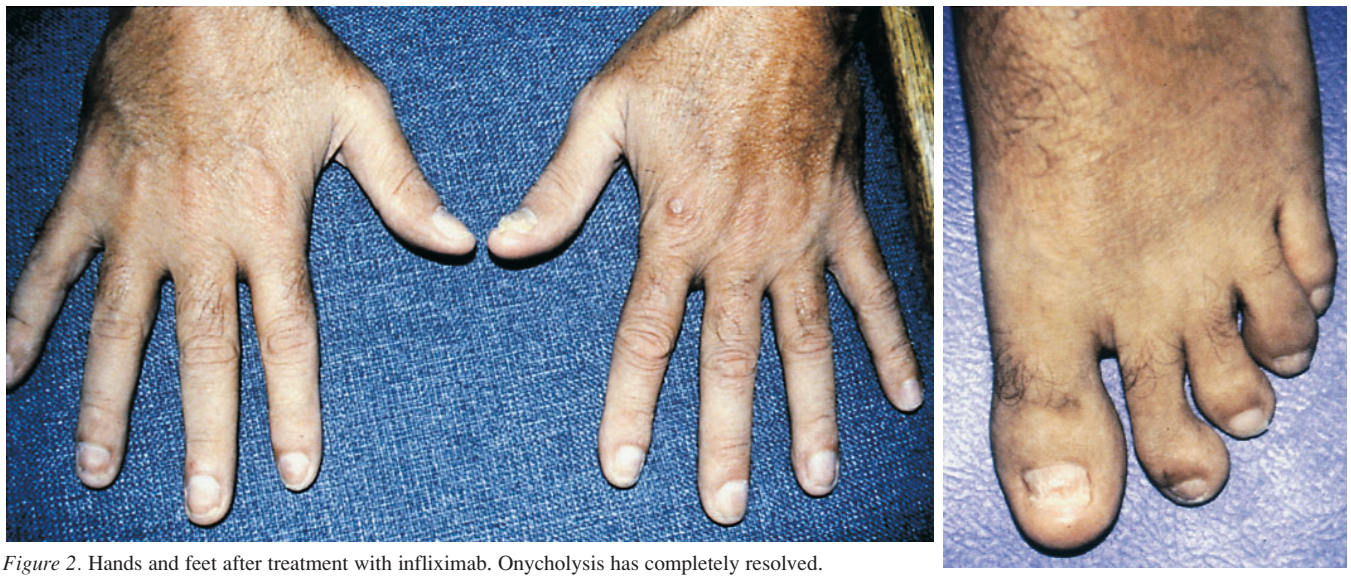

Figure 2. Hands and feet after treatment with infliximab. Onycholysis has completely resolved.

protein that also inhibits TNF-α, effectively treated HIV associated PsA and reduced TNF-α levels[39]. In addition, etanercept treatment has been reported to result in marked symptom improvement in patients with undifferentiated or reactive arthritis[40]. A recent study reported the downregulation of TNF-α synthesis in patients with RA treated with infliximab[41]. Finally, infliximab decreased TNF-α concentrations in 6 patients with HIV[42].

This case report showed the use of anti-TNF-α therapy in treating HIV associated Reiter's syndrome. Initially, the patient was partially responsive to a combination of corticosteroid therapy and MTX. However, after about 3 months he became unresponsive to this treatment regimen. He was subsequently given an infliximab and MTX regimen that significantly attenuated the signs and symptoms of Reiter's syndrome. Importantly, this regimen was well tolerated. To date, treatment with infliximab every 6 to 7 weeks has resulted in almost complete resolution of the signs and symptoms of Reiter's syndrome. Further studies are required to fully characterize the safety of anti-TNF-α therapy in HIV positive and potentially immunocompromised patients.

Because TNF plays an important role in the immune and inflammatory responses, inhibition of TNF may suppress defense mechanisms against infections. The suppression of these mechanisms may be exacerbated in patients with already compromised immune systems, such as patients with HIV. Indeed, the 2 approved anti-TNF agents, infliximab and etanercept, both contain warnings in their labeling pertaining to the potential for infections and the need to discontinue these agents if a serious infection develops. In a recent report, etanercept treatment in an HIV patient with PsA was halted due to recurrent polymicrobial bacterial infections including *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa,* despite marked improvements in his psoriasis and PsA[39]. Keane, *et al*[43] recently reported a higher incidence of tuberculosis infections in infliximab treated patients compared with background incidence rates. Although exhibiting anergy to the tuberculosis skin test prior to therapy, our HIV patient who was treated with infliximab did not develop an infection. Importantly, his CD4+ levels remained within the normal range (359–1519 cells/mm^3). Because the risk of opportunistic infection is highest in HIV patients with CD4+ counts < 200 cells/mm^3, CD4+ levels should be monitored in all HIV patients treated with anti-TNF therapy[44,45]. The physician needs to weigh the risks with the potential benefits of anti-TNF therapy in these high risk patients.

In addition to inhibiting the signs and symptoms of Reiter's syndrome and other TNF-α mediated rheumatic disorders associated with HIV infection, infliximab may reduce HIV replication through blockade of TNF-α receptors and TNF-α synthesis[46]. Whether infliximab in combination with the antiretroviral therapy had a synergistic effect on suppressing HIV viral load in this case is unknown.

To date, our patient has not experienced any immune function impairment or opportunistic infections. Further study of the efficacy of infliximab in the treatment of HIV associated Reiter's syndrome and other arthropathies and the potential synergistic effects of antiretroviral and anti-TNF-α therapy is warranted.

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