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CASE REPORT

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Septic arthritis of the right ankle caused by *Staphylococcus aureus* infection in a rheumatoid arthritis patient treated with etanercept

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Abstract We report on a 65-year-old man with rheumatoid arthritis who developed septic arthritis of the right ankle and was treated with etanercept, low-dosage prednisolone, and salazosulfapyridine for 18 weeks. *Staphylococcus aureus* was cultured from ankle synovial fluid; hence, etanercept was stopped and cefazolin was administered. The patient responded well to arthroscopic synovectomy and irrigation of the ankle. Etanercept treatment should cease if it leads to septic arthritis and patients should be prescribed systemic antibiotics, with surgical debridement considered.

Key words Arthroscopy · Rheumatoid arthritis · Septic arthritis · *Staphylococcus aureus* · Tumor necrosis alpha antagonist

Introduction

Etanercept is a fully humanized soluble tumor necrosis factor (TNF) receptor–IgG1 fusion protein that binds to both soluble and membrane-bound TNF. It thereby inhibits the interaction of TNF with cell surface receptors and prevents TNF-mediated cellular responses. Multiple studies and large-scale trials have demonstrated the efficacy of anti-TNF blockers in the treatment of rheumatoid arthritis (RA).[1,2] Although the inflammatory response is suppressed, lowering of TNF activity to below critical levels can cause serious adverse effects in some patients.[3] We describe here a case of septic arthritis of the ankle caused by *Staphylococcus aureus* infection in a patient receiving etanercept, corticosteroid, and salazosulfapyridine treatment for RA. The patient was informed that the data concerning his case would be submitted for publication.

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Case report

A 65-year-old Japanese man presented with a 6-year medical history of RA, and bilateral arthroscopic synovectomy of the knees performed 4 years earlier without concomitant infection. There was no history of smoking or alcohol use. He had a body weight of 68 kg and a height of 163 cm. His current medications included daily administration of 7.5 mg prednisolone, 1000 mg salazosulfapyridine, 300 mg sulindac, 150 mg teprenone, and 300 mg isoniazid. Eighteen weeks earlier he had started a twice-weekly subcutaneous administration of 25 mg etanercept. This was well tolerated and offered sufficient control of disease activity. Before administration of etanercept, C-reactive protein (CRP) levels were 8.03 mg/dl, erythrocyte sedimentation rate (ESR) was 100 mm/h, and DAS28[4] was 5.17. Hepatitis B and C serology were negative, and tuberculin skin testing was positive. The patient was not receiving methotrexate treatment. Inflammatory signs decreased after administration of etanercept, the levels of CRP were 0.34 mg/dl, ESR was 17 mm/h, and DAS28 was 3.31.

In February 2006, the patient presented with a 2-day history of swelling, redness, and worsening pain in his right ankle. On initial examination, the patient's temperature was 36.9°C and pulse and blood pressure were normal. There was pain, swelling, and redness of the right ankle joint with a decreased range of motion. Ten milliliter yellow turbid synovial fluid was aspirated from the ankle for laboratory analysis. Etanercept treatment was stopped immediately, and intravenous cefazolin was prescribed for 2 weeks. Prednisolone and salazosulfapyridine treatment were continued at the same dosage.

Laboratory data revealed a white blood cell count of 12 000/mm^3 (segmented neutrophils 84%), a hemoglobin level of 12.0 g/dl, and elevated inflammatory markers (ESR 40 mm/h, CRP 24.8 mg/dl). X-ray films of the right ankle joint revealed spreading of the talotibial joint space and erosive destruction of the subtalar joint (Fig. 1). Magnetic resonance imaging of the right ankle revealed synovitis and joint fluid collection (Fig. 2). Culture of the synovial fluid

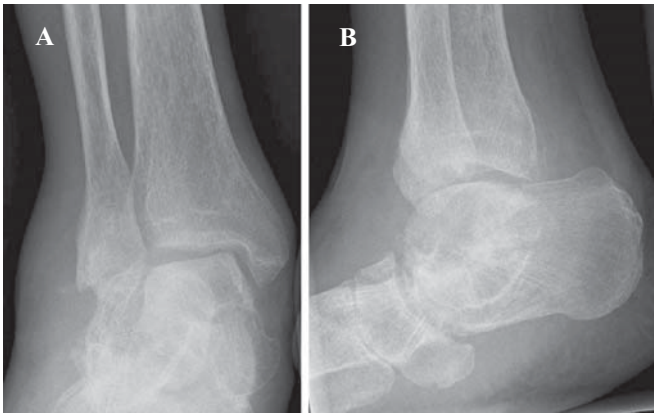

Fig. 1. Radiograph of the patient's right ankle. Talotibial joint space shows spread and severe subtalar joint destruction caused by rheumatoid arthritis

from the right ankle yielded growth of *S. aureus*, which was sensitive to cefazolin. Blood cultures were negative.

Arthroscopic synovectomy, debridement, and irrigation of the right ankle were performed on the same day. Joint irrigation was continued for 11 days, after which repeated aspiration of fluid from the ankle revealed no latent staphylococcal infection. A histological section of synovial tissue showed acute inflammatory infiltrate (Fig. 3). The patient's symptoms improved and he was discharged 4 weeks later. He remains well, with no evidence of recrudescence of the joint sepsis 10 months later.

Discussion

Rheumatoid arthritis is an autoimmune disease that can be treated with immunosuppressive agents and corticosteroids. However, the rise in incidence of infection as a complication of RA has paralleled the use of such drugs.[5] Septic arthritis is a common complication that occurs in 0.3%–3% of RA patients,[5] and *S. aureus* has been the causative organism in 75% of reported cases.[5,6] It is unclear whether the increase in infection is caused solely by the use of immunosuppressive drugs and corticosteroids, or whether RA predisposes patients by injuring the joint capsule and facilitating the entry of bacteria.

In post-marketing surveillance of etanercept treatment in Japan, serious septic arthritis was reported in six cases (0.11%) up to June 2005. Mor et al.[7] reported on relapsing oligoarticular septic arthritis during etanercept treatment of RA, and advised that the use of TNF blockades be discontinued during prolonged antimicrobial therapy. The rheumatology study group of the Ministry of Health, Labor, and Welfare, Japan has developed guidelines for the safe use of etanercept in Japan.[8] The group emphasizes that etanercept is contraindicated in patients with active infections or a history of serious infections within the past 6 months. It is important that patients with acute infections discontinue etanercept and undergo aggressive treatment.[9]

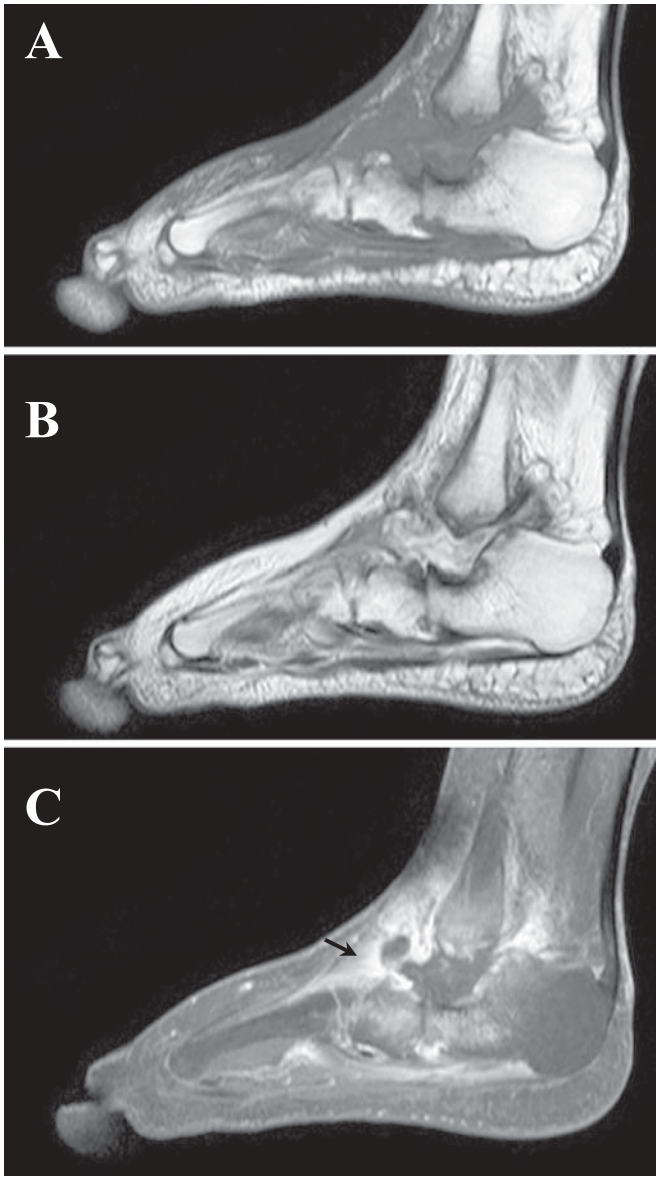

Fig. 2. Magnetic resonance imaging of the right ankle. Sagittal T1 (**A**) and T2-weighted sequences (**B**) show marked effusion. (**C**) Contrast media enhancement of the diffusely enlarged and thickened synovia (*arrow*) following intravenous administration of gadolinium

A Japanese phase II clinical study of 147 patients who were refractory to conventional disease-modifying antirheumatic drugs revealed a significantly better ACR20 response in those patients receiving 12 weeks of a twice-weekly dosage of 10 mg or 25 mg, compared with the placebo group. This trend was similar in both the ACR50 and ACR70 responses.[8] Although Bathon et al.[10] reported that twice-weekly therapy of 25 mg etanercept is both safe and efficient in elderly (≥65 years) RA patients, we suspect that the twice-weekly subcutaneous administration of 25 mg etanercept was too high for the patient in the present study.

In spite of improved antimicrobial therapy and supportive care, septic arthritis remains a true medical emergency and the cause of significant morbidity and mortality.[11] Once the diagnosis of septic arthritis is suspected, the initiation

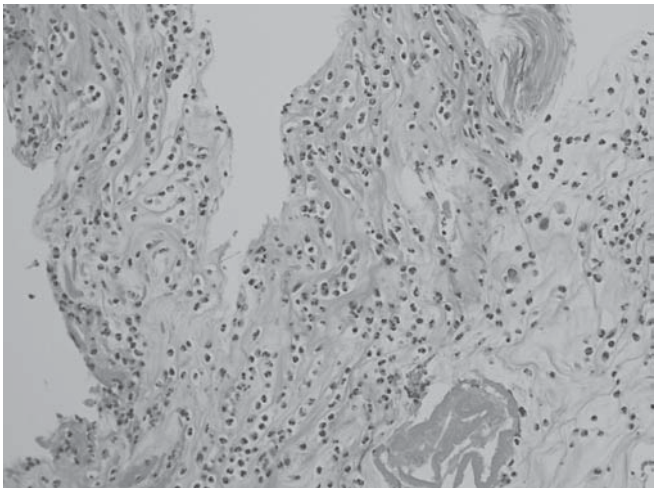

Fig. 3. Polymorphonuclear leukocytic infiltration of synovial tissue (hematoxylin–eosin, ×100)

of treatment should not be delayed. Most authors recommend prompt arthroscopic irrigation and debridement, and intravenous antibiotic treatment once cultures have been obtained.[12–14] In addition, the diagnosis of septic arthritis may be delayed in etanercept self-injection patients, because of similarities to an exacerbation of RA. It is imperative that practitioners be aware of these infectious risks when treating patients with TNF blockers.

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