Case Report

Septic Arthritis Caused by *Actinobacillus ureae* in a Patient with Rheumatoid Arthritis Receiving Anti-Tumor Necrosis Factor-α Therapy

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ABSTRACT. *Actinobacillus ureae*, formerly known as *Pasteurella ureae*, is a rare human pathogen. We describe a case of septic arthritis and abscess formation caused by this unusual organism in a patient with rheumatoid arthritis, who was being treated with tumor necrosis factor-α inhibitors. (J Rheumatol 2004;31:1663–5)

Key Indexing Terms:
SEPTIC ARTHRITIS
RHEUMATOID ARTHRITIS
ACTINOBACILLUS UREAE
TUMOR NECROSIS ALPHA INHIBITORS

Actinobacillus ureae, previously known as *Pasteurella ureae*, was initially identified in 1960. It is an unusual commensal of the human respiratory tract[1]. However, it has been isolated as a principal pathogen in patients with meningitis, endocarditis, bacteremia, atrophic rhinitis, bronchitis, pneumonia, conjunctivitis, peritonitis[1], and otitis media[2]. It has been associated with bone marrow infection in a patient with rheumatoid arthritis (RA)[3], infection of an ocular prosthesis[4], and meningitis in a patient positive for human immunodeficiency virus (HIV)[5]. Most of these cases had a predisposing factor such as head trauma, a neurosurgical procedure, liver cirrhosis, alcoholism, diabetes, malnutrition[1], or immunosupression (HIV)[5].

Etanercept is a dimeric fusion protein consisting of an extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor (TNF) receptor linked to a Fc portion of human IgG1. It is a competitive inhibitor of TNF at the cell surface receptor and regulates the biologic activity of TNF. Infections have been observed in patients with RA taking etanercept[6]. We describe a case of septic arthritis and abscess formation with *A. ureae* in a patient with RA treated with etanercept and methotrexate (MTX). This is the first reported case of septic arthritis and abscess formation with *A. ureae* in the English medical literature based on a thorough Medline search.

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CASE REPORT

A 59-year-old woman with a history of RA with overlap features of limited systemic sclerosis presented with intense pain and swelling of her right elbow and knee. Her symptoms developed shortly after returning from a trip to Kenya, where she visited a game reserve and suffered a fall. She suffered from several abrasions over her right forearm, elbow, and knee and developed redness, swelling, and tenderness of these areas. She did not have a fever or other constitutional symptoms and was treated with nonsteroidal antiinflammatory drugs (NSAID) and topical ointments in Kenya. Her current medications included MTX, etanercept, nifedipine, lanzoprazole, and pamidronate. She was taking both MTX and etanercept regularly before, during, and after her trip. On initial examination she had a temperature of 100.3°F, with normal pulse and blood pressure. Positive physical findings included a holosystolic murmur at the left upper sternal border. Healing abrasions with no open or draining wounds were noted over the right lateral forearm, one inch below the elbow joint, and also over the anterior aspect of the right knee. There was pain and swelling of the right elbow joint with flexion limited to 90°. There was associated fluctuance of the medial portion, induration of the lateral aspect and surrounding erythema, as well as swelling of the olecranon bursa. The right knee was warm, red, tender, and swollen, with a 30° flexion contracture. Tenderness and mild swelling were also appreciated along the popliteal fossa. Peripheral white blood cell count was 23,800 billions/liter. MTX and etanercept were withheld and intravenous cefazolin and ciprofloxacin were started. Magnetic resonance imaging (MRI) of the right upper extremity revealed changes due to RA, with substantial pannus formation with 2 large cystic collections tracking into the forearm, suggestive of synovial cysts or abscesses (Figure 1). MRI of the right lower extremity showed 3 separate collections representing abscesses in the gastrocnemius (Figure 2) and peroneal longus muscles along with enhancement of synovium of the knee joint. There was evidence of knee synovitis due to either RA or a septic joint, and infectious peroneal tenosynovitis. During irrigation and debridement of the elbow and forearm, it was noted that the elbow joint was filled with gross pus that dissected into the distal forearm and tracked medially across the joint. The region of fluctuance on the medial aspect was also found to be filled with pus that tracked proximally and distally, involving the fascial planes between the flexor and extensor musculature. A subtotal synovectomy of the right elbow was performed. Surgical exploration of the right knee revealed mildly inflamed synovium with pannus formation without evidence of gross pus. Partial synovectomy, thorough irrigation and debridement, and closure of the arthrotomy were performed. This was

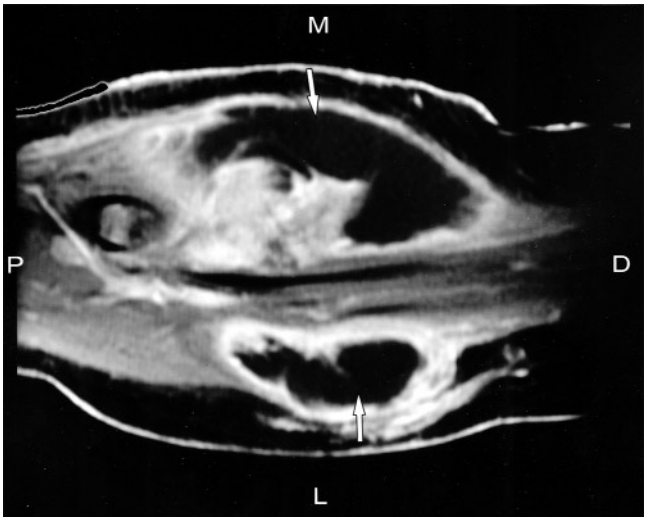

Figure 1. MRI showing sagittal view of right forearm with arrows pointing towards the cystic collections tracking into the forearm. M: medial, L: lateral, P: proximal, D: distal end of the right forearm.

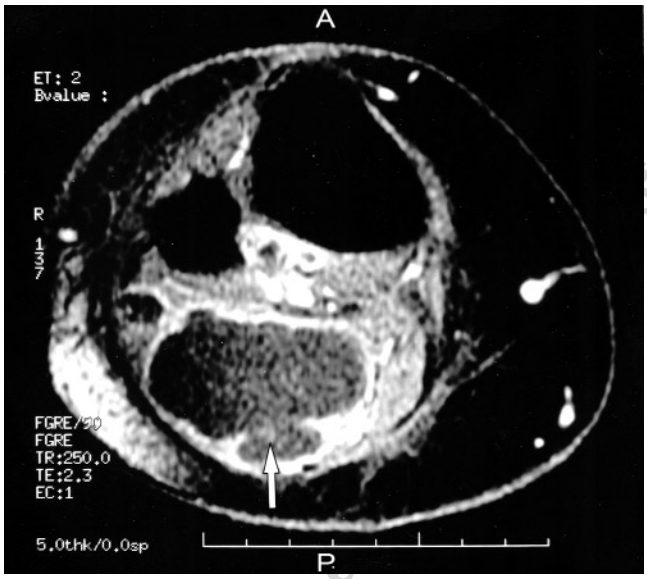

Figure 2. MRI axial view of the right lower extremity beneath the right knee joint with arrow pointing towards rim enhancing collection in the lateral gastrocnemius. A: anterior, P: posterior view of the right lower extremity.

followed by exploration and drainage of the popliteal fossa and gastrocnemius abscess. A large amount of gross pus was appreciated in the fascial interval between the lateral head of the gastrocnemius and the soleus, dissecting throughout and extending distally to the midcalf region and proximally into the popliteal fossa. Unlike the right elbow, it did not appear that there was communication between the purulent abscesses and the right knee joint.

The wound culture from the right elbow had moderate growth of *A. ureae*. Blood cultures were negative. Her antibiotics were changed to intravenous piperacillin/tazobactam and ciprofloxacin. Due to the extensive collections tracking into the musculature and significant purulent and necrotic material, the patient required repeat debridement and irrigation of the wounds. Her hospital course was complicated by left lower lobe pneumonia and a flare of RA. Her joint symptoms were controlled with NSAID. MTX was reintroduced and she was transferred to a rehabilitation unit while taking oral ciprofloxacin. Total duration of antibiotic therapy was 6 weeks.

DISCUSSION

RA is an autoimmune disease and its treatment involves the use of immunosuppressive agents and corticosteroids. The incidence of infections as a complication of RA has paralleled the use of corticosteroids and immunosuppressive agents. Pulmonary infections, skin sepsis, and pyarthrosis are the most common infections[7,8]. Septic arthritis with unusual organisms in patients with RA has been reported in the literature. Some of these include septic arthritis with *Prevotella bivia*[9], *Mycobacterium malmoense*[10], *Brucella*[11], and *Listeria*[12].

Etanercept is a TNF-α blocker used in the treatment of RA. Since the approval of etanercept in August 2000, infections have accounted for 21% of adverse effects reported to the US Food and Drug Administration. Infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms in postmarketing experience with etanercept. Infections have been noted in all organ systems and have been reported in patients receiving etanercept alone or in combination with immunosuppressive agents. A variety of opportunistic infections were seen during etanercept therapy including herpes zoster, fungal infections, herpes simplex, and *Candida*. A small number of cases of tuberculosis, *Pneumocystis carinii* pneumonia, aspergillosis, and cryptococcosis were also seen. One case of histoplasmosis and one case of listeria sepsis have been reported[6].

A. ureae is a small, non-motile, vacuolated, pleomorphic organism and is gram negative. It is most often a harmless commensal. Usually an underlying or predisposing condition such as postsurgical infection, diabetes, periodontal disease, emphysema, and alcohol related cirrhosis of the liver are associated with infections caused by *A. ureae*. Cases of meningitis have been associated with previous trauma (assault, cranial surgery)[1] and underlying immunosuppressive disease[5]. Only one case of bone marrow infection caused by *A. ureae* in RA has been reported[3]. The patient, who developed bone marrow infection with *A. ureae*, was a mild drinker with RA. He had low grade fevers, normocytic anemia, and high erythrocyte sedimentation rate; investigations included bone marrow aspirate. The bone marrow aspirate was nonspecific, but the culture grew *A. ureae*. He was treated with intravenous benzyl penicillin 24 million units per day for 2 weeks and then switched to oral tetracycline for 2 weeks[3].

A. ureae strains are susceptible to most antimicrobials including ampicillin, cephalothin, cefoxitin, tetracycline, aminoglycosides, and trimethoprim-sulfamethoxazole.

Penicillin is favored as first-line antibiotic for invasive disease, followed by erythromycin and third-generation cephalosporins.

In our patient with RA, treatment with immunosuppressants, MTX, and etanercept in the setting of trauma led to a spontaneous infection with *A. ureae*, probably the commensal of her respiratory tract.

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