Case Report

Primary Cutaneous *Nocardia otitidiscaviarum* Infection in a Patient with Rheumatoid Arthritis Treated with Infliximab

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ABSTRACT. Anti-tumor necrosis factor-α (anti-TNF-α) therapy strategies result in significant clinical benefits in patients with rheumatoid arthritis, but with an increased rate of serious infectious diseases. We describe a patient receiving infliximab who developed a primary cutaneous *Nocardia otitidiscaviarum* infection after a skin injury. (J Rheumatol 2005;32:2432–3)

Key Indexing Terms:
SKIN INFECTION *NOCARDIA OTITIDISCAVIARUM* RHEUMATOID ARTHRITIS
INFLIXIMAB ANTI-TUMOR NECROSIS FACTOR-α

Anti-tumor necrosis factor-α (TNF-α) treatment strategies result in significant clinical benefits in patients with rheumatoid arthritis (RA), but with an increased rate of serious infectious diseases[1,2]. We describe a patient receiving infliximab who developed a primary cutaneous *Nocardia otitidiscaviarum* infection after a skin injury.

CASE REPORT

We describe a 70-year-old white man with RA (first diagnosed in 1974) who was treated with infliximab (3 mg/kg) for 3 years, as well as methotrexate (20 mg/week) and corticosteroids. He was diagnosed with insulin-dependent diabetes in 1985. Two weeks before the 18th infusion of infliximab he was injured while gardening, and had a deep wound in his right palm. The hand lesion was not inflamed, but an erythematous papular lesion appeared on the anterior side of his right forearm. Two weeks later the lesion spontaneously drained and formed a cutaneous nonpainful ulcer covered by white pus, with erythematous periphery (Figure 1). There was no fever or asthenia at any time. *N. otitidiscaviarum* was subsequently isolated from the ulcer and biological samples showed inflammation. A computerized tomographic scan did not detect any other septic localization (particularly in the brain or the lungs). Infliximab therapy was withdrawn. He was then treated with combination ofloxacin and clindamycin antibiotic therapy for 3 months. Twenty days later the skin ulcer was completely healed.

DISCUSSION

Nocardia infection is a rare opportunistic bacterial infection. Nocardia species are aerobic actinomycetes, nonmotile, non-spore-forming filamentous Gram-positive bacteria. A model for *N. brasiliensis* infection in mice in which a granuloma is produced with large numbers of foam-laden macrophages has been established. Macrophages contain organisms in various stages of degeneration within their cytoplasm[3]. Monocytes/macrophages play an important role in host defense both by their direct microbial capacity and by their synthesis of cytokines such as TNF-α[4]. Silva, *et al* detected TNF-α activity in sera from a BALB C mouse at all stages of *N. brasiliensis* infection[5]. Treatment with antiserum against TNF significantly enhanced the experimental infection in the animal's spleen and liver. Nocardiocidal

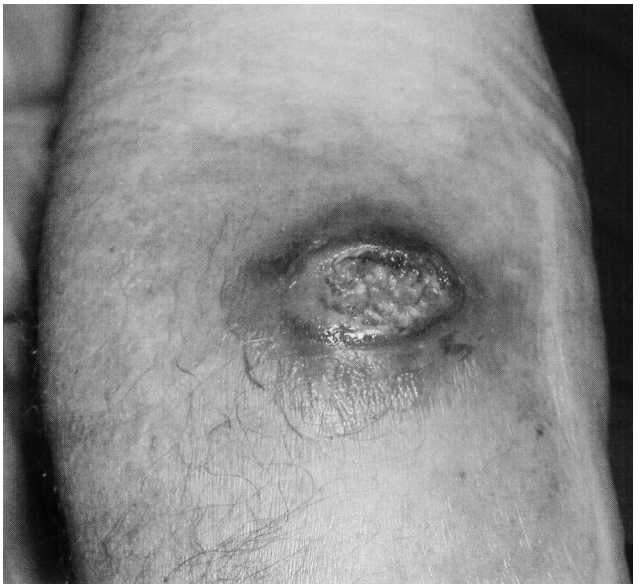

Figure 1. Cutaneous nonpainful ulcer covered by white pus, with erythematous periphery, on the anterior side of the right forearm.

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activity in peritoneal macrophages obtained from infected mice was evaluated *in vitro* and was significantly reduced following anti-TNF antiserum treatment[5]. These data suggest a role for TNF in resistance to *N. brasiliensis* infection.

This rare infection occurs primarily in immunocompromised hosts (immunosuppressive therapies, transplant recipients, HIV-positive patients, malignancy)[6]. Infection is initiated most commonly by inhalation of bacteria present in dust or soil. Rarely, infection may result from ingested contaminated food or by traumatic inoculation. Inhalation of *N. asteroides* is the most common cause of human nocardiosis (80%). Most of the time it starts by bronchopneumonia localization (75%), and results in systemic dissemination in 50% of cases (lungs, brain, and skin)[7]. Primary localized cutaneous and subcutaneous nocardiosis are less common (25% of cases). Cutaneous nocardiosis is usually caused by *N. brasiliensis* and *N. otitidiscaviarum*[8]. *N. otitidiscaviarum* is an infrequent cause of infection in humans and is believed to be less pathogenic than the more common species of nocardia. *N. otitidiscaviarum* can cause all 3 subtypes of primary cutaneous nocardiosis, and most frequently superficial skin infections including abscess, ulcers, and wound infections[9]. Most other cases of *N. otitidiscaviarum* infection have not been well documented[10]. Generally, this form is underdiagnosed, because the required culture incubation is not routinely done[11,12]. Delay in diagnosis is common. Definitive diagnosis requires isolation and identification of the organism from a clinical specimen. Nocardia species are slow-growing organisms, and colonies may be visible only after 6–8 days of incubation.

Nocardiosis is usually treated with trimethoprim-sulfamethoxazole for 6 weeks for limited infection to more than 12 months for a severe disease; however, *N. otitidiscaviarum* and *N. farcinica* strains are resistant to this antibiotic[13,14].

Although cases of *N. asteroides* have been described using anti-TNF-α therapy (9 with infliximab, 2 with etanercept)[15,16], ours is the first report of primary non-spreading, cutaneous nocardia due to *N. otitidiscaviarum*. In our case direct inoculation of bacteria through the skin and its track along lymph node chains were clearly identified, with no dissemination. The patient's diabetes and concomitant treatment with prednisone and methotrexate may have also been contributory. *N. otitidiscaviarum* is resistant to standard therapy with sulfamide. Efficient treatment was accomplished with ofloxacin and clindamycin.

Anti-TNF-α therapy increases the risk of serious infectious diseases. Our case confirms the specific risk of nocardia infection. Primary cutaneous nocardia infection can occur after injury to the skin and contamination with soil. Even if bacterial prevalence is a key consideration in making a diagnosis, it is important to consider this slow-growing bacteria so that laboratory cultures can be kept beyond the usual 5 days. It is important to initiate appropriate treatment quickly before systemic dissemination occurs, which can have dramatic consequences.

REFERENCES

1. Ellerin T, Rubin RH, Weinblatt ME. Infections and anti-tumor necrosis factor alpha therapy. Arthritis Rheum 2003;48:3013-22.
2. Food and Drug Administration. Safety update on TNF-alpha antagonists: infliximab and etanercept. Food and Drug Administration, Center for Biologics Evaluation and Research. Arthritis Advisory Committee Meeting, August 17, 2001. Washington, DC: Food and Drug Administration.
3. Folb PI, Jaffe R, Altmann G. Nocardia asteroides and Nocardia brasiliensis infections in mice. Infect Immun 1976;13:1490-6.
4. Beutler B, Cerami A. Cachectin and tumour necrosis factor as two sides of the same biological coin. Nature 1986;320:584-8.
5. Silva CL, Faccioli LH. Tumor necrosis factor and macrophage activation are important in clearance of Nocardia brasiliensis from the livers and spleens of mice. Infect Immun 1992;60:3566-70.
6. Dominguez DC, Antony SJ. Actinomyces and nocardia infections in immunocompromised and nonimmunocompromised patients. J Natl Med Assoc 1999;91:35-9.
7. Corti ME, Villafane-Fioti MF. Nocardiosis: a review. Int J Infect Dis 2003;7:243-50.
8. Kageyama A, Yazawa K, Ishikawa J, et al. Nocardial infections in Japan from 1992 to 2001, including the first report of infection by Nocardia transvalensis. Eur J Epidemiol 2003;19:383-9.
9. Hui CH, Au VW, Rowland K, Slavotinek JP, Gordon DL. Pulmonary nocardiosis re-visited: experience of 35 patients at diagnosis. Respir Med 2003;97:709-17.
10. Clark NM, Braun DK, Pasternak A, Chenoweth CE. Primary cutaneous Nocardia otitidiscaviarum infection: case report and review. Clin Infect Dis 1995;20:1266-70.
11. McNeil MM, Brown JM. The medically important aerobic actinomycetes: epidemiology and microbiology. Clin Microbiol Rev 1994;7:357-417.
12. Scott WW Jr, Kuhlman JE. Focal pulmonary lesions in patients with AIDS: percutaneous transthoracic needle biopsy. Radiology 1991;180:419-21.
13. Boiron P, Provost F. In-vitro susceptibility testing of Nocardia spp. and its taxonomic implication. J Antimicrobiol Chemother 1988;22:623-9.
14. Berkey P, Moore D, Rolston K. In vitro susceptibilities of Nocardia species to newer antimicrobial agents. Antimicrob Agents Chemother 1998;32:1078–9.
15. Wallis RS, Broder M, Wong J, Beenhouwer DO. Granulomatous infections due to tumor necrosis factor blockade: correction. Clin Infect Dis 2004;39:1254-5.
16. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 2004;38:1261-5. Epub 2004 Apr 15.