Disseminated Sporotrichosis Associated with Treatment with Immunosuppressants and Tumor Necrosis Factor–α Antagonists

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We report a case of disseminated sporotrichosis in a 49-year-old man who was treated with multiple immunosuppressants, including tumor necrosis factor (TNF)–α antagonists (etanercept and infliximab), for presumed inflammation arthritis. This case illustrates the potential for infectious complications related to the use of cytotoxic immunosuppressants and anticytokine agents, such as TNF-α antagonists.

We report a case of disseminated sporotrichosis in a 49-year-old man who was treated with multiple immunosuppressants, including TNF-α antagonists (etanercept and infliximab), for presumed (but misdiagnosed) psoriatic and rheumatoid arthritis. This case illustrates the obvious importance of making the correct diagnosis prior to initiating potentially life-threatening immunosuppressive therapy and the need for an increasing appreciation of the potential for infectious complications related to the use of cytotoxic immunosuppressants and anticytokine agents, such as TNF-α antagonists.

Case history. A 49-year-old man from Spokane, Washington, with a history of psoriasis was in his usual state of health until October 2000, when he began to have increasing pain and swelling of his left knee. Joint aspiration showed predominantly neutrophilic inflammation. Cultures of aspiration fluid were sterile. The patient was treated with ibuprofen and sulfasalazine for presumed psoriatic arthritis. His knee symptoms worsened, and he underwent multiple knee aspirations; cultures of all aspirate samples were sterile. Methotrexate therapy was started for what was interpreted as worsening psoriatic arthritis.

In late October, the patient developed left-side forearm edema, olecranon bursitis, and tenosynovitis. He underwent aspiration of the olecranon bursa, which also showed neutrophilic inflammation, but culture of aspirate fluid was sterile. The patient was treated with prednisone (10 mg q.d.). In November and December, the pain and swelling of the hands and wrists worsened; the patient developed nodular lesions on his arms and left leg, and therapy was started with etanercept, a TNF receptor linked to the Fc portion of human IgG1 (Enbrel; Immunex). The patient’s condition showed no improvement, and the diagnosis of rheumatoid arthritis was considered, because the results of testing for rheumatoid factor were weakly positive (titer of 1:4). He was scheduled to undergo a skin biopsy of his nodular lesions but missed his appointment.

In January 2001, the patient began to receive leflunomide (Arava; Aventis), a disease-modifying antirheumatoid drug thought to prevent the expansion of activated lymphocytes, and subsequently he was treated with infliximab, an anti–TNF-α antibody (Remicade; Centocor). His hand and arm lesions began to ulcerate, and, in late January 2001, he was admitted to an outside hospital for further evaluation and treatment. His prednisone dosage was increased to 25 mg b.i.d. He underwent biopsy of 1 of the forearm lesions; culture of the biopsy specimen and pathologic findings revealed Sporothrix schenckii infection. The prednisone dosage was gradually reduced, other immunosuppressive drug treatment was stopped, and treatment with itraconazole (200 mg po b.i.d.) was started.

The patient continued to develop new nodular lesions on his extremities that began to ulcerate. He underwent extensive debridement of his hands and left foot multiple times (figure 1). Multiple cultures yielded S. schenckii. Although the patient had evidence of disseminated cutaneous and osteoarticular disease, no pulmonary or other visceral disease was demonstrated on CT scans. In early February 2001, the patient began to receive therapy with amphotericin B, which was subsequently changed to amphotericin B lipid complex, 5 mg/kg q.d. (Abelcet; The Liposome Company), because of renal toxicity. He continued to have worsening lesions on his arms and legs and was transferred to our hospital (Harborview Medical Center, Seattle) for further management. Further review of his history revealed that he lived on a 10-acre farm with numerous wild rose bushes and that, in October 2000, he had been scratched numerous times on his arms and legs. He also reported years of heavy alcohol use; he consumed ~1 gallon of whiskey per
week. He continued to receive amphotericin B lipid complex (5 mg/kg q.d.) and itraconazole (200 mg iv b.i.d.) for 4 weeks. There was progressive improvement of the lesions, and the patient was discharged from the hospital and continued to receive itraconazole (oral solution; 200 mg b.i.d.). He underwent skin grafting on both hands 1 month later.

Discussion. Sporotrichosis (historically known as Beurmann’s disease or Schenck’s disease) [1, 2] is caused by *S. schenckii*, a dimorphic fungus commonly found in soil, plants, or decaying plant matter, and classically is associated with exposure to rose thorns. Exposure is generally believed to occur via direct inoculation with the organism. Various clinical syndromes have been associated with *S. schenckii* infection, including cutaneous sporotrichosis, extracutaneous sporotrichosis (osteoarticular, pulmonary, ocular, sinus, kidney, testes, and epididymis infection, as well as meningitis), and multifocal extracutaneous (disseminated) sporotrichosis [3, 4]. Disseminated sporotrichosis is rare in immunocompetent hosts, but it can occur in individuals with underlying immunosuppression. Although disseminated sporotrichosis has been most described most widely in patients with AIDS [5], there are scattered reports of the disease in patients with other immunosuppressive

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**Figure 1.** A, Left upper extremity of the case patient after extensive debridement due to disseminated sporotrichosis. B, Sporotrichoid nodular lesions.
conditions, such as malignancies, solid-organ transplants, and chronic liver disease.

Studies of host immune responses to invasive fungal infections, including *S. schenckii* infection, have suggested an important role for innate humoral and cell-mediated immunity [6]. In mouse models of *S. schenckii* infection, TNF appears to play an important role in immunological control [7–9], suggesting a mechanism by which TNF-α antagonists might predispose a person to infection by *S. schenckii* and lead to disseminated sporotrichosis.

To our knowledge, this is the first case of disseminated sporotrichosis related to treatment with TNF-α antagonists (in this case, etanercept and infliximab). We hypothesize that, in this patient, alcohol use, extensive exposure to rose bushes, and progressive immunosuppression (including treatment with prednisone, disease-modifying antirheumatic drugs [methotrexate and leflunomide], and TNF-α antagonists) prescribed for (misdiagnosed) arthritis resulted in progressive sporotrichosis.

Treatment with TNF-α antagonists has been associated with serious fungal, mycobacterial, and bacterial infections. Warris and colleagues [10] recently reported a case of invasive pulmonary aspergillosis associated with infliximab therapy in a 25-year-old man with Crohn disease complicated by fistulas. In response, Keenan et al. [11] reported that 6 cases of aspergillosis, 5 cases of *Pneumocystis carinii* pneumonia, 3 cases of histoplasmosis, 1 case of coccidioidomycosis in a septic joint, 3 cases of systemic *Candida* infection, and 5 cases of systemic unspecified fungal infections occurred in patients receiving infliximab since that drug was approved by the US Food and Drug Administration (FDA) in 1998. It was noted that, in almost all of these cases, there was concurrent immunosuppression, including therapy with corticosteroids, azathioprine, methotrexate, or mercaptopurine. In addition, Keane et al. [12] reported 70 cases of tuberculosis associated with infliximab treatment, and Wagner et al. [13] reported 1 case of gastrointestinal tuberculosis misdiagnosed as Crohn disease that was exacerbated by infliximab treatment. There have also been reports of bacterial infections, including listeriosis [14] and fatal pneumococcal sepsis [15], associated with use of anti-TNF-α agents. Finally, an FDA surveillance report on etanercept published in 1999 [16] documented that 30 of the estimated 25,000 patients treated with etanercept developed serious infections, including sepsis, and that 6 of these patients died. In addition, a controlled study of etanercept treatment for sepsis showed a higher incidence of death among patients treated with etanercept than among patients treated with placebo [17].

We believe this case illustrates some important points. (1) It is obviously important to make the correct diagnosis prior to initiating potentially life-threatening immunosuppressive therapy. (2) We need an increasing appreciation of the potential for infectious complications related to the use of TNF-α antagonists. (3) Immunosuppressive regimens that contain both cytotoxic and anticytokine agents may make individuals more prone to infectious complications than either of these classes of agents would if used alone. We suggest that this newly recognized entity—namely, a severe or disseminated infection in a patient receiving cytotoxic and anticytokine agents—might be aptly referred to as “cytotoxic anticytokine infection syndrome.”

**References**