Listeria-Associated Arthritis in a Patient Undergoing Etanercept Therapy: Case Report and Review of the Literature

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Listeriosis can be a cause of infectious arthritis. Here, we present a case of articular listeriosis in a patient with rheumatoid arthritis receiving treatment with etanercept, a tumor necrosis factor antagonist. We review the literature of articular listeriosis and discuss the role of tumor necrosis factor blockade in precipitating listeriosis.

CASE REPORT

In January 2002, a 54-year-old Caucasian woman presenting with a painful swelling of the right shoulder joint was admitted to the rheumatology ward. Apart from a largely unremarkable medical history (appendectomy and severe postoperative bleeding following a cesarean section in 1982), the patient had suffered from seropositive rheumatoid arthritis since 1998. Diagnosis of rheumatoid arthritis was made within the first 6 months of disease and was based upon fulfilling all except one (rheumatoid nodules) of the American College of Rheumatology criteria for the diagnosis of rheumatoid arthritis. The first disease-modifying antirheumatic drug (DMARD) therapy was sulfasalazine, which was later terminated due to elevated liver function tests. Next, the patient was treated with cyclosporine, which was terminated because of high blood pressure and followed by methotrexate. Because of nausea, methotrexate dosage was never increased beyond 12.5 mg/week. The patient then elected to participate in an interleukin-10 study protocol, which was stopped after 6 months because of insufficient improvement. In February 2001, she began receiving 25 mg of etanercept (Enbrel), a tumor necrosis factor alpha (TNF- α) blocker, subcutaneously twice weekly, which was well tolerated and offered sufficient control of disease activity. Five months later, however, acute swelling of the right shoulder joint started. Because septic arthritis was suspected, etanercept was replaced by oral prednisolone, and the joint was tapped several times. Cultures, however, remained sterile. Because of chronic swelling of the right shoulder joint, the patient was referred to our department 5 months later.

At presentation, the right shoulder joint was swollen and tender, with decreased range of motion. No redness or local elevation of the skin temperature was found. No fever was detectable and no night sweats were reported. The heart rate was 88/min, and blood pressure was 160/70 mm Hg. Laboratory evaluation found elevated acute-phase reactants (erythrocyte sedimentation rate, 83 mm/h; C-reactive protein, 3.56 mg/dl).

Plain X-ray films of both shoulder joints were unremarkable (Fig. 1A). Sonography of the right shoulder revealed synovitis and chronic bursitis. Magnetic resonance imaging showed massive joint effusions in the subacromial and subdeltoid bursa (Fig. 1B and C). Because septic arthritis was suspected, arthrocentesis of the swollen right shoulder was performed and 70 ml of moderately cloudy inflammatory synovial fluid was aspirated and positively cultured for *Listeria monocytogenes* sensitive to aminopenicillins. Culture was performed on Columbia CNA agar with 5% sheep blood (Becton Dickinson Microbiology Systems, Cockeysville, MD), and identification of *L. monocytogenes* was done by API-Listeria kit (Biomerieux, Marcy l'Etoile, France). Consequently, antibiotic therapy with intravenous ampicillin (2 g three times daily) was started. Four additional arthrocenteses were performed, the first of which was again positive for *L. monocytogenes*, whereas the following three remained sterile. Blood cultures remained sterile throughout the observation period. As soon as the patient recovered, synovectomy and bursectomy were performed and a large cystic structure filled with granulomatous and necrotic masses within the rotator cuff was removed, leaving the joint largely unaffected. The patient recovered quickly and rapidly regained mobility of her right shoulder. DMARD therapy with methotrexate (15 mg/week) was initiated. The patient remained clinically stable and was discharged 1 week later.

This case illustrates infectious arthritis caused by *L. monocytogenes* in a patient treated with the TNF- α blocker etanercept, which is a fusion protein of the human TNF- α receptor 2 and the Fc portion of human immunoglobulin G. *L. monocytogenes* is a gram-positive, facultatively intracellular bacillus that can be isolated from a large number of environmental sources. *Listeria* infection is relatively rare, with an estimated 2,500 cases per year in the United States. It mostly affects debilitated patients, such as those with cancer, the immunosuppressed, such as transplant recipients, and the elderly. Whereas immunocompetent individuals usually present with nonspecific flu-like symptoms, lymphadenopathy, and gastrointestinal symptoms, immunocompromised individuals can develop meningoencephalitis and sepsis, with an overall mortality as high as 15 to 30% (39). Furthermore, in pregnant women, infection

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FIG. 1. Imaging of the right shoulder. (A) Plain radiograph of the right shoulder shows marked joint effusion but otherwise normal appearance of the bone and joint space. (B and C) Magnetic resonance examination of the right shoulder. Axial GE T1 weighted sequence (B) shows marked effusion of the subdeltoid bursa. After intravenous administration of gadolinium, contrast media enhancement of the diffusely enlarged and thickened synovia (arrows) (C).

with *L. monocytogenes* can be transmitted to the fetus, leading to septicemia and fetal loss. The majority of sporadic cases are associated with *Listeria* contamination of unpasteurized dairy products, although other modes of transmission may also be involved. Rare epidemic cases of listeriosis have also been traced to exposure to contaminated food (12).

Infectious arthritis caused by *L. monocytogenes* is a rare event. A review of the literature revealed 29 reported cases (1, 2, 4, 5, 7–9, 11, 13, 14, 19, 25–27, 30–33, 35, 36, 40, 41, 43, 45, 47) (Table 1). The median age was 55 years (range, 22 to 80 years). Typically, disease emerged as monoarthritis of a large

joint, such as the hip or knee, whereas only 9 cases involved more than one joint. The majority of these patients suffered from underlying diseases, such as rheumatic diseases, diabetes mellitus, and cancer, or had undergone organ transplantation. These conditions as well as their therapeutic management led to profound alterations of the immune system, which facilitate infection with *L. monocytogenes*. In addition, the presence of prosthetic joints appears to increase the likelihood for articular *Listeria* infection, since approximately two-thirds of cases occurred in prosthetic joints. *Listeria* arthritis was very unusual (1 out of 29 patients) in subjects without any underlying disease

TABLE 1. Summary of the reported cases of arthritis due to infection with *Listeria monocytogenes*^a

Case	Reference	Age	Sex	Underlying disease	Prosthetic joint	Affected joint region	Medication	Outcome
1	40	NR	F	Rheumatoid arthritis	NR	NR	Infliximab	NR
2	11	69	M	Rheumatoid arthritis	Yes	Knee	None	Cure
3	5	64	F	Rheumatoid arthritis	Yes	Knee	None	Cure
4	27	71	M	Rheumatoid arthritis	Yes	Knee	None	Cure
5	8	NR	NR	Rheumatoid arthritis	Yes	Oligoarticular	NR	NR
6	30	64	F	Rheumatoid arthritis	No	Ankle	Methotrexate	NR
7	47	77	M	Rheumatoid arthritis	No	Hip	Yttrium-90 ^c	Unrelated death
8	35	74	F	Rheumatoid arthritis	No	Shoulder/knee	Glucocorticoids, methotrexate	Cure
9	26	63	M	Psoriatic arthritis	No	Knee	Methotrexate	Cure
10	19	22	F	Lupus erythematosus	Yes	Knee	Methotrexate	Cure
11	1	37	F	Renal transplantation	Yes	Hip	Glucocorticoids	Cure
12	14	29	M	Renal transplantation	Yes	Hip bilateral	Glucocorticoids, azathioprin	Cure
13	13	29	M	Renal transplantation	Yes	Hip	Glucocorticoids, azathioprin	Cure
14	45	66	M	Diabetes mellitus	Yes	Hip	None	Cure
15	7	66	M	Diabetes mellitus	No	Knee	None	NR
16	36	80	F	Colon cancer	Yes	Knee	None	Cure
17	25	49	M	Multiple myeloma	NR	Knee bilateral	Glucocorticoids	Cure
18–22 ^d	43	NR	NR	NR	Yes	Oligoarticular	NR	Cure
23	9	70	M	None ^b	Yes	NR	None	NR
24	4	66	M	None	Yes	Hip	None	Cure
25	41	73	M	None	Yes	Hip	None	NR
26	2	64	F	None	Yes	Hip	None	Cure
27	31	70	M	None	Yes	Hip	None	Cure
28	32	37	M	None	No	Knee	None	Cure
29	33	40	M	None	NR	NR	None	NR

^a NR, not recorded; F, female; M, male.

^b This patient had a previous *Listeria septicemia* infection.

^c Intraarticular yttrium-90 radiosynoviothetesis.

^d Includes five cases.

FIG. 2. *Listeria* infection in 31 patients treated with infliximab and etanercept. The x axis indicates the percentage of total. (A) Type of TNF- α blocker. (B) Indication of TNF- α blocker. (C) Manifestation of *Listeria* infection. (D) Concomitant medication. Other immunosuppressive drugs include azathioprine and mercaptopurine. Three patients with methotrexate received combination therapy (one each with hydroxychloroquin, mycophenolat mofetil, and cyclosporine A). (E) Outcome of *Listeria* infection. Note that categories C and D contain overlapping factors.

or with a negative history of joint replacement, supporting the concept that immune suppression and/or joint prosthesis are critical factors for susceptibility to articular *Listeria* infection. Outcomes were generally good. In about half of the cases, treatment with intravenous antibiotics followed by surgical intervention resulted in complete resolution of symptoms.

Immunity to *Listeria* infection is complex; antigen-specific T cells that produce macrophage-activating cytokines, such as gamma interferon, are thought to play a significant role. However, there is evidence for other important factors involved, since athymic mice can initially protect themselves against *Listeria* infection and since human immunodeficiency virus-infected patients appear not to be at an increased risk for listeriosis (18). In contrast, mice treated with steroids were predisposed to *Listeria* infection (28), and the administration of methotrexate resulted in increased *Listeria* multiplication (42). TNF- α , which mediates macrophage activation, is considered to be important for immunity against *L. monocytogenes* (16, 17, 29, 37). Aside from playing a central role in the pathogenesis of inflammatory and erosive joint disease, the physiological function of TNF- α is strongly involved in the defense against pathogens, intracellular pathogens in particular (10). Several points of evidence from experimental animal models and clinical studies support this concept. Experimental models have shown that a sublethal infectious challenge with *Listeria* leads to a local increase in the production of TNF- α in the infected organ (16). If TNF- α production is blocked, these animals fail to survive, whereas substitution of recombinant TNF- α yields excellent protection against *Listeria* infection (17). It is presently unclear how TNF- α and other cytokines, like interleukin-1 and interleukin-6, gamma interferon, and macrophage colony-stimulating factor, affect *Listeria* infection. However, T-cell-dependent immunity does not appear to be critical, since TNF- α is protective and TNF- α blockade also increases the severity of *Listeria* infection in T-cell-deficient mice (17).

In addition, much of the knowledge of the role of TNF in host defense has been gained as a result of infections emerging upon clinical use of TNF- α blocking agents. Beneficial as TNF- α blockers have turned out to be for a variety of rheumatic diseases, their efficiency in blocking TNF- α also clearly increases the risk for infections like tuberculosis, histoplasmosis, or listeriosis, as well as the risk of an accelerated and severe course of these infections (21–24, 46). Moreover, there is evidence that severe bacterial infections, noncandida fungal infections, and hepatitis B are among those that are commonly kept under control with the help of TNF- α (44). Listeriosis is one of the opportunistic infections which has a higher incidence in patients treated with TNF- α inhibitors. In 2001, the Food and Drug Administration's postlicensure safety surveillance of TNF- α antagonists listed 12 cases of listeriosis after treatment with TNF- α antagonists (38). Thus, *Listeria* infection is still a relatively rare event in patients receiving TNF- α blockers. However, its severity, as illustrated by the fact that 5 (41%) out of these 12 patients had a fatal outcome, makes it clinically important. So far, 31 cases of *L. monocytogenes* infections under TNF- α -neutralizing agents have been described in the literature (3, 6, 15, 20, 34, 40) (Fig. 2). Twenty-eight cases were associated with infliximab (Remicade), a chimeric antibody against human TNF- α , and three cases were associated with etanercept treatment. TNF- α blocker therapy was initiated for rheumatoid arthritis in 18 cases, inflammatory bowel disease in 9 cases, and juvenile rheumatoid arthritis and psoriatic arthritis in 1 patient each. For two patients, the indication for infliximab is unknown. Eight patients (26%) died from the infection. The most common clinical manifestations were septicemia (60%) and meningitis (50%).

Infectious complications with *Listeria* were observed more frequently in patients undergoing infliximab treatment than etanercept treatment (38, 40). This can be attributed to several different factors, and our understanding is still not complete enough at the moment to decide their relative weights. Apart

from pharmacological differences concerning the way to block TNF- α by using either soluble receptors, such as etanercept, which also block lymphotoxin-beta and preferentially bind the soluble form of TNF- α , or antibodies, such as infliximab, which bind both soluble and transmembrane TNF- α but not lymphotoxin-beta, environment-based factors need to be considered. For instance, the apparently higher rate of tuberculosis infection upon infliximab treatment might be due to the fact that most patients treated with etanercept live in the United States, where tuberculosis is by far less common than in Europe, while infliximab has been more frequently used worldwide outside the United States. Thus, the increased probability of a history of exposure could therefore also be a variable contributing to higher numbers of *Listeria* infection with infliximab than with etanercept. Nevertheless, reports of *Listeria* infection upon etanercept treatment are rare, and *Listeria* arthritis has so far been reported only for a patient receiving infliximab therapy for rheumatoid arthritis (40).

In summary, the reported case of *Listeria* arthritis in a patient undergoing etanercept and corticosteroid therapy without concomitant methotrexate points to the need for a higher index of suspicion of intracellular infections in rheumatoid arthritis patients treated with anti-TNF- α drugs. Infection with *L. monocytogenes* can clearly occur during etanercept treatment and is a diagnostic challenge.

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