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【 CASE REPORT 】

Listeria monocytogenes Ankle Osteomyelitis in a Patient with Rheumatoid Arthritis on Adalimumab: A Report and Literature Review of *Listeria monocytogenes* Osteomyelitis

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Abstract:

Localized *Listeria* infection predominantly occurs in the prosthetic and hip joints. We herein report a case of *Listeria monocytogenes* ankle osteomyelitis in a 73-year-old man receiving adalimumab who was transferred to our hospital because of suspected rheumatoid arthritis (RA) flare. He reported a four-month history of left ankle swelling. A surgical biopsy revealed *L. monocytogenes* osteomyelitis in the left tibia and talus bones. The patient was successfully treated with antibiotics and surgical debridement. Thus, infection due to *L. monocytogenes* can present as ankle osteomyelitis in immunocompromised patients and may mimic an RA flare.

Key words: *Listeria monocytogenes,* osteomyelitis, tumor necrosis factor (TNF)-alpha inhibitor, adalimumab, rheumatoid arthritis

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Introduction

Tumor necrosis factor (TNF)-alpha inhibitors are widely used to treat autoimmune diseases such as rheumatoid arthritis (RA), inflammatory bowel disease, ankylosing spondylitis, and psoriasis (1). Bacterial, mycobacterial, fungal or viral infections are a known, potentially serious adverse effect of these drugs. *Listeria monocytogenes* meningitis, sepsis, and septic arthritis in patients using TNF-alpha inhibitors have been reported, but little is known about *L. monocytogenes* ankle osteomyelitis associated with adalimumab treatment (1-4).

We herein summarize and compare eight *L. monocytogenes* osteomyelitis cases from the literature with our own case.

Case Report

A 73-year-old man with a 15-year history of RA was transferred to our hospital for the assessment of a possible RA flare. His medical history included suspected tuberculous lymphadenitis, ischemic heart disease, and dyslipidemia but no pneumocystis pneumonia or cytomegalovirus infection. He exhibited left ankle swelling for 4 months and gait difficulties due to pain but no diarrhea. He was administered 40 mg of adalimumab every 2 weeks for 7 months. In addition, his RA was controlled with methylprednisolone (8 mg/day) and iguratimod (50 mg/day). His diet comprised pasteurized milk and cheese daily and only common raw foods, such as vegetables and fish, consumed in Japan.

On an examination, the patient's vital signs were normal. He had a well-defined 4-cm mass superficial to the medial malleolus of his left ankle. The mass was not tender or

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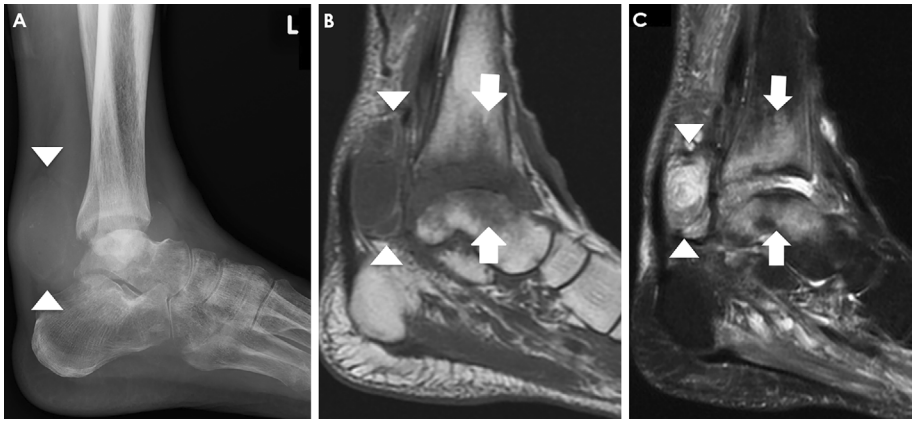

Figure 1. **(A) X-ray findings show granulation around the ankle joint (white arrowheads). (B) MRI findings show a decreased T1 signal in the tibia and talus (white arrows) and granulation (white arrowheads). (C) MRI findings further show an increased fat-suppressed T2 signal in the tibia and talus (white arrows) and granulation (white arrowheads). MRI: magnetic resonance imaging**

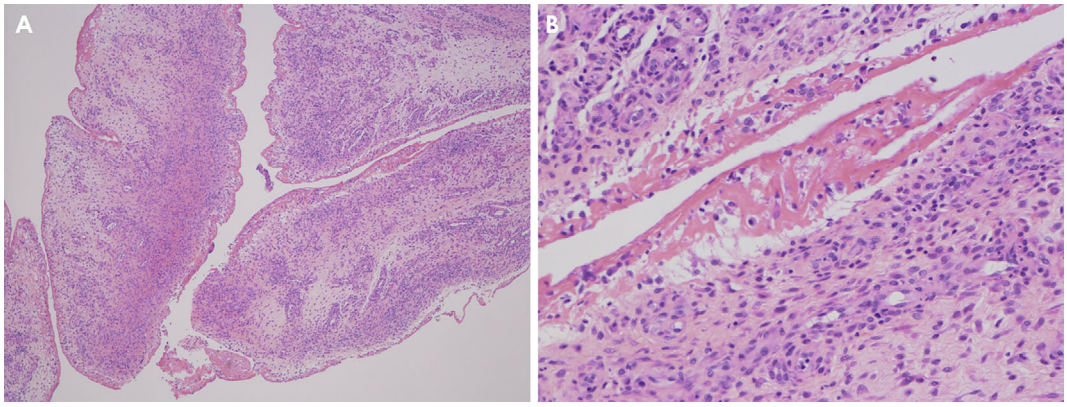

Figure 2. **Pathological images of the synovial membrane (A) (×40) and (B) (×200) show neutrophilic infiltration without caseating necrosis.**

erythematous, but mild limitation of range of motion in the left ankle joint and pain during walking were observed. The remaining examination findings were normal.

Blood tests showed an elevated white blood cell count (16.7×10^3/μL; neutrophils 81%, lymphocytes 7%, monocytes 7%, eosinophils 1%, and basophils 0%) and C-reactive protein (CRP) (17.6 mg/dL). Plain radiographs suggested granulation of the left tibia and talus bones (Fig. 1). Magnetic resonance imaging (MRI) showed a decreased T1 signal in the tibia and talus and granulation and increased fat-suppressed T2 signal in the tibia, talus, and granulation (Fig. 1). Blood cultures were repeatedly negative. Based on his use of the immunosuppressants and history of suspected tuberculous lymphadenitis, we initially suspected tuberculosis osteomyelitis and thus discontinued the adalimumab and iguratimod treatments. To make a definite diagnosis, surgical biopsies of the distal tibia, talus, and mass in the ankle were performed, and their culture revealed the presence of *L. monocytogenes*. A pathological examination revealed neutrophilic infiltration in the adjacent bone and synovial membrane (Fig. 2) and *L. monocytogenes* abscess in the mass. There were no signs of caseating epithelioid granulomas. An analysis of the synovial fluid was culture-negative.

We diagnosed him with *L. monocytogenes* osteomyelitis and initiated intravenous ampicillin (2 g, 6 hours) and gentamycin (90 mg, 8 hours) on day 14. On day 24, the affected bone was resected, and cement fixation was performed. Gentamycin was discontinued on day 29 (duration: 16 days). His initial erythrocyte sedimentation rate (ESR) after admission was 109 mm/h on day 29. As the symptoms improved with the removal of the infected bone and the ESR decreased to 40 mm/h, which were considered in previous reports to meet the criteria for osteomyelitis being cured or antibiotics being terminated (5-7), ampicillin treatment was discontinued on day 80 (duration: 66 days). We performed a second operation on day 143 to remove the cement and transplant autogenous iliac bone graft as a substitute (Fig. 3). He slowly recovered completely, and his gait returned to normal. There has been no recurrence of infection for three years.

Discussion

Our case indicates that *L. monocytogenes* infection can

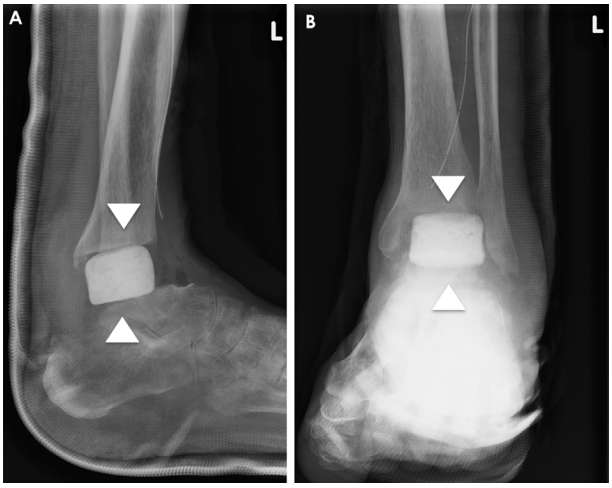

Figure 3. X-ray findings show surgical resection of the affected bone and cement fixation (white arrowheads) in the (A) lateral view and (B) posterior to anterior view.

occur in the non-prosthetic ankle bone of a patient at a high risk of *L. monocytogenes* infection treated using adalimumab and may mimic an RA flare.

L. monocytogenes ankle osteomyelitis is a rare manifestation. *L. monocytogenes* is a small, aerobic, Gram-positive, non-encapsulated bacillus that can cause central nervous system infection, sepsis, and gastroenteritis (8-10). In certain cases, *L. monocytogenes* causes localized infections (8-10). Among the 43 retrospective cases studied, *L. monocytogenes* joint and bone infections mainly occurred in the hip (60%) and prosthetic joints (84%) (11). *L. monocytogenes* osteomyelitis is even rarer, and only 10 cases have been reported (11-18). Patient characteristics were not described in two cases (11). We have summarized the distribution of infection in our case along with that in the other eight cases in Table (12-18). There were four spinal infections-two in the tibia, one in the femur, and one in the proximal phalanx-in addition to the infection in the tibia and talus in our case (12-18). Only one patient had a prosthetic joint (12). Our patient and six others had underlying or predisposing conditions, such as leukemia in two cases, diabetes mellitus in two cases, and RA in one case (12-16). The mean age was 67.8±13.7 years old (12-18). Our patient and two others reported an intake of dairy products (13, 17). Three patients in total (including ours) were undergoing immunosuppressive therapy (12, 14).

L. monocytogenes ankle osteomyelitis can occur in patients at a high risk for *L. monocytogenes* infection and undergoing adalimumab treatment. Reported risk factors for *L. monocytogenes* infection include pregnancy, old age, immunocompromising conditions, malignancy, immunosuppressive therapy, and dairy product consumption (19, 20). Even in pasteurized milk, post-pasteurization contamination and the probable survival of *L. monocytogenes* are known to cause infections (21, 22). In addition, TNF-alpha inhibitors increase the risk of *L. monocytogenes* infection (4, 23). They inhibit the activation and differentiation of macrophages and phagosome formation, which play important roles in the clearance of intracellular pathogens, such as *Mycobacterium tuberculosis* and *L. monocytogenes* (1). The incidence rate of *L. monocytogenes* infection in patients with RA treated using TNF-alpha inhibitors is 0.27-0.30 per 1,000 patient-years, which is 75 times greater than that observed in the general population (23, 24). Among TNF-alpha inhibitors, adalimumab and infliximab have a higher risk of infection due to *M. tuberculosis* than etanercept (24). Nevertheless, whether there is increased risk of *L. monocytogenes* osteomyelitis from adalimumab over other TNF-alpha antagonists is not known. Furthermore, although osteomyelitis was not observed, the risk of septic arthritis in patients with RA treated using TNF-alpha inhibitors was highest in the early months of therapy (25). In fact, our case developed the symptoms three months after starting adalimumab. In contrast, the risk of infection increases with longer steroid use (26). Similarly, our case had been treated for RA for 15 years. In addition, our patient may have had arthritis owing to the possibility of a false-negative *L. monocytogenes* in the joint fluid culture and the findings of synovial inflammation.

In addition, *L. monocytogenes* osteomyelitis can mimic an RA flare and hence may be misdiagnosed in patients with RA. The symptoms of an RA flare closely resemble those of osteomyelitis in terms of the presence of a fever, fatigue, pain, and swelling (27, 28). Based on our case and previously published cases, 44.4% (4/9) of the patients experienced pain or swelling involving the hand or foot. However, there are some indications to help differentiate between these two presentations. For example, RA flares may be prone to occur rapidly and typically resolve within one to two weeks, but *L. monocytogenes* osteomyelitis may tend to present insidiously (12-16, 27-29). Among 43 cases of *L. monocytogenes* joint and bone infections, 73% were subacute or chronic in their onset, developing over more than 7 days (11). In our case comparison, 66.7% (6/9) of cases also presented with a subacute or chronic onset, and the mean duration from the onset to a hospital visit was 53.4±55.6 days (12-18). In addition, *Listeria* infection tends to involve a single bone compared with an RA flare (12-18, 27-29). As mentioned in the previous paragraph, a detailed medical history to evaluate the risk factors for *Listeria* infection may prove helpful (4, 19, 20, 23). Some diagnostic tests are also important to differentiate between the two conditions. However, non-specific markers of inflammation tend to be found in both conditions, as the ESR and CRP are elevated in both *Listeria* infection and RA, and the ferritin changes in infection or non-infectious inflammation have not been well determined owing to inconsistent findings among studies (30, 31). Nevertheless, the following findings in imaging studies are helpful for diagnosing osteomyelitis: 1) MRI findings of extensive and intense bone marrow changes (32-34) and 2) ultrasound findings of subcutaneous edema, subcutaneous power Doppler signal changes, and periosteal vascularity (35). Finally, a biopsy is crucial for the final diagnosis. In fact, in our patient, the medical history,

Table. **Characteristics of Patients with Listeria Monocytogens Osteomyelitis.**

Case [Ref]	Age Sex	Co-morbidities	Pregnancy	Food consumption	Immunosuppressant	Prosthetic joint involvement	Chief complaint	Duration of symptoms	Location	Culture			Treatment		Response to treatment
										Blood	Bone	Others	Surgery	Antibiotic therapy	
1 [12]	57 M	DM, asthma	(-)	NA	Corticosteroid	(-)	Progressive back pain	3 weeks	T5	NA	(+)	NA	(+)	Ampicillin and tobramycin sulfate for 6 weeks	At follow-up six months after completion of therapy, the patient was well and without evidence of recurrent infection.
2 [12]	70 M	Total hip replacement, previous *Listeria* bacteremia, mitral valve replacement, and previous rheumatic heart disease	(-)	NA	NA	(+)	Right hip pain	5 months	Rt.Hip	(-)	(+)	Rt. Femoral canal (+)	(+)	Ampicillin and tobramycin sulfate for 2 weeks => oral amoxicillin trihydrate for 7 months	The patient remained free of complaints for seven months after hospital discharge
3 [13]	69 M	Previous spinal laminectomy	(-)	Pate and unpasteurized cheeses	NA	(-)	Back pain	5 months	L5-S1	(-)	NA	Epidural abscess (+)	(+)	Vancomycin and ceftriaxone	NA
4 [14]	54 F	Acute lymphoblastic leukemia	(-)	NA	6-mecaptopurine cyclophosphamide methotrexate	(-)	Right lower leg pain, fever, rigors, erythema 8 cm×3 cm over the lower third of her right tibia	2 days	Rt. Tibia	(+)	NA	NA	(-)	Gentamicin, fucidin, and penicillin => Penicillin and erythromycin for 3 months	The pain gradually subsided over the sub-sequent six weeks of treatment and the patient became asymptomatic.
5 [16]	43 M	Chorionic lymphoblastic leukemia	(-)	NA	NA	(-)	Painful swelling of the left 4th finger	1 month	Lt. 4th proximal phalanx	(-)	(+)	Aspiration of the swollen area (+)	(-)	Oral trimethoprim-sulfamethoxazole for 6 weeks	The left 4th finger improved over the six weeks of treatment and showed minimal swelling without pain or tenderness.
6 [12]	74 F	DM, HTN, Obesity, CKD and chronic venous insufficiency	(-)	NA	NA	(-)	Left ankle pain	10 days	Lt. Talus	NA	(+)	NA	(-)	Ampicillin for 1 month => oral ciprofloxacin	The patient was well when he was discharged from the hospital after one month of ampicillin treatment.
7 [17]	92 M	HTN, HF, arrhythmia, gastric ulcer, and hip arthroplasty	(-)	Raw milk and raw cheese	None	(-)	Fever and acute lower back pain	1 week	L4-S1	(+)	NA	NA	(-)	Amoxicillin for 6 days and gentamicin for 4 days => oral cotrimoxazole for 3 months	At the three-month clinical assessment, the patient had been recovering slowly and regaining mobility.
8 [18]	79 M	Bilateral hernia repair with mesh, bilateral subclavian to carotid artery bypass and repair of an endovascular infrarenal abdominal aortic aneurysm, HTN, dyslipidemia, gout, reflux, smoker	(-)	No consumption of processed meats, cheeses or other dairy products.	None	(-)	Acute, progressively worsening right-sided back pain radiating to the right groin and anterior thigh	3 weeks	L3-L4	(+)	(-)	(-)	(-)	Ampicillin for 6 weeks	The patient rapidly improved over the treatment. The patient was subsequently seen in follow-up at 2- and 6-month time points with on- going clinical recovery and no recurrence of disease.
9 [Present]	73 M	RA	(-)	Pasteurized milk and cheese	Corticosteroid, adalimumab, and iguratimod	(-)	Left ankle swelling	4 months	Lt. Tibia and talus	(-)	(+)	Lt. Ankle joint aspiration (-)	(+)	Gentamycin for 3 weeks and ampicillin for 14 weeks	The patient slowly made a complete recovery and his gait returned to normal. There has been no recurrence of his infection for three years.

Ref: reference number, DM: diabetes mellitus, HTN: hypertension, CKD: chronic kidney disease, RA: rheumatoid arthritis, HF: heart failure, NA: not available, (+): positive, (-): negative

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MRI results, and biopsy findings greatly contributed to the final diagnosis.

In conclusion, *L. monocytogenes* osteomyelitis in the ankle can occur in patients with RA receiving adalimumab and may mimic an RA flare. Since TNF-alpha inhibitors are widely used, it is important to consider checking for infection, including *L. monocytogenes*, in patients presenting with joint or bone pain. Further research is necessary to determine whether or not such missed infections may be more common than previously considered.

The authors state that they have no Conflict of Interest (COI).

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