Osteomyelitis and arthritis of the wrist caused by Mycobacterium intracellulare in an immunocompetent patient: a case report and literature review

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ABSTRACT

Mycobacterium intracellulare causes infection in humans. Involvement of joint and bone, however, is extremely rare. We present the case of an immunocompetent 67-year-old female with chronic swelling of the wrist joint diagnosed as rheumatoid arthritis by her previous physician. Examination revealed an unclosed fistula associated with a puncture, and bone and joint destruction on radiographs. She was diagnosed with osteomyelitis and arthritis due to M. intracellulare on histological and microbiological examinations. She was successfully treated with radical surgical debridement and anti-tuberculous drugs for 1 year and there was no recurrence at 3 years postoperatively.

Keywords: *Mycobacterium intracellulare*; Osteomyelitis; Arthritis; Wrist

INTRODUCTION

Non-tuberculous mycobacterium (NTM) is widely distributed in nature and some of its species have been reported to cause infection in human beings[1]. NTM infection of the upper extremity is rare, and commonly involves the tenosynovium[2-4]. Involvement of a joint and bone is extremely rare; there have been a few reports of this type of involvement in immunocompetent cases[2,5]. We report the case of an immunocompetent patient with wrist joint and bone infection caused by *Mycobacterium intracellulare* and reviewed the literature.

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CASE REPORT

A 67-year-old Japanese woman (right-handed) visited our department with swelling and discharge from a fistula of the right wrist. Her job involved managing a bar. She had no relevant past medical conditions and no family history of infectious disease and denied a history of trauma or overuse.

She noticed mild right wrist pain about ten years ago and the wrist swelling about three months before visiting our hospital. She visited a local clinic and was treated for rheumatoid arthritis. After conservative treatment, including various drug regimens (unknown), she visited another hospital because her condition did not improve. At the hospital, her wrist was punctured for examination. However, the puncture hole did not close and the discharge from the fistula continued.

Physical examination revealed swelling of the dorsal aspect of the right wrist and discharge from the fistula on the ulnar side of the wrist (Figure 1a). There was no evidence of a tendon rupture or a peripheral nerve disorder. In addition, other joints were not swollen or painful. The grip strength for the right and left hands, measured with a Jamar digital dynamometer (Takei Scientific Instrument Co, Ltd., Niigata, Japan), were 15.6 Kg and 23.5 Kg, respectively. The respective range of motion for the right and left extremities, measured with a standard goniometer, was as follows: wrist dorsiflexion, 25° and 45°; wrist palmar flexion, 30° and 75°; forearm pronation, 70° and 90°; and forearm supination, 60° and 90°. Plain radiographs of the right wrist revealed narrowing of the radiocarpal joint (RCJ), cystic change in the distal radius and ulna and widening of the distal radioulnar joint (DRUJ) (Figure 1b). The irregularity of the cortex of ulnar side of metaphyseal ulna which was near to the fistula was also found, and this finding guided us suspicion of infection.

As the fistula had not closed in a few months, we

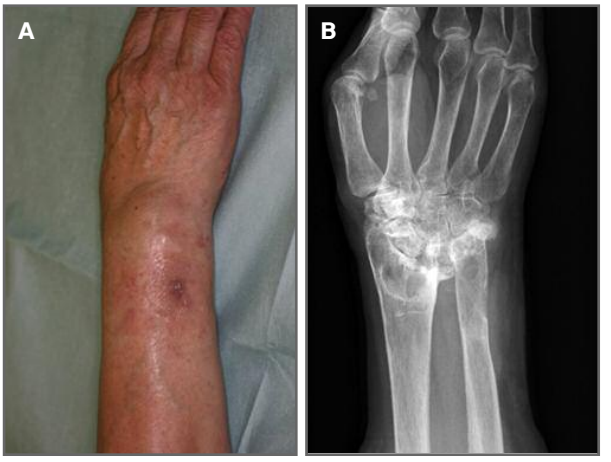

FIGURE 1. Preoperative appearance and plain radiograph of the right wrist. **A**) Swelling of the dorsal and ulnar sides; a fistula was found on the ulnar side of the right wrist. **B**) Plain radiograph of the right wrist showed narrowing of the radiocarpal joint, cystic change in distal radius and ulna, discontinuity of the ulnar cortex of distal ulna, and widening of the distal radioulnar joint. The irregularity of ulnar cortex of distal ulna was near to the fistula

performed further examinations under suspicion of an infection. The patient's blood examination revealed a white blood cell count of 6230 cells/mm3, erythrocyte sedimentation rate of 21 mm/hr, CD4-positive lymphocyte count of 1056 cells/mm3, C-reactive protein level of 0.11 mg/dL; the rheumatoid factor, anti-cyclic citrullinated peptide antibody, antinuclear antibody, QuantiFERON TB-2G (Japan BCG Laboratory Co., Ltd, Tokyo, Japan), and human immunodeficiency virus antibody were negative. Gram, Ziehl-Neelsen, fluorescent and fungal staining of the discharge were also negative. Cultures of the discharge were proven to be negative for aerobic and anaerobic bacterium, fungus and mycobacterium in four weeks in the preoperative period. The polymerase chain reaction (PCR) test for *Mycobacterium tuberculosis*, *M avium*, and *M intracellulare* (TaqMan-PCR, Roche Diagnostics K. K., Tokyo, Japan) was negative. There was no abnormal finding on a plain radiograph of the chest. Magnetic resonance imaging (MRI) of the right wrist revealed a pathological lesion with low signal intensity in T1 weighted-image (WI) and high signal intensity in T2 WI in the bone marrow in the distal radius and ulna, RCJ, DRUJ, and subcutaneous tissue in ulnar side of the wrist (Figure 2a and 2b). Moreover, signal intensity of distal ulna and subcutaneous lesion was almost the same and the subcutaneous lesion was continuing to the ulnar fistula through the discontinuity of the cortex of ulna (Figure 2a). This discontinuity of the cortex of metaphyseal ulna made us suspicion of osteomyelitis.

To obtain a definite diagnosis, a radical resection of

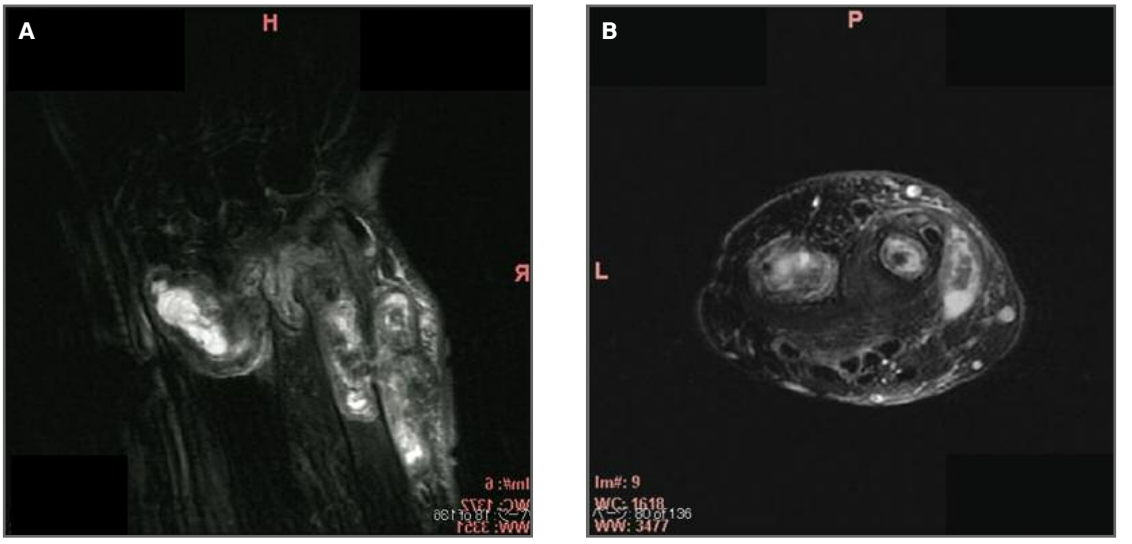

FIGURE 2. Preoperative MRI of the right wrist. **A**) Coronal image with fat-suppression (chemical shift selective method, CHESS). The mass with increased signal intensity was found in the distal radius and ulna, distal radio-ulnar joint, and under the subcutaneous tissue. The ulnar mass continued from the ulna to the fistula. **B**) Sagittal image with fat-suppression (CHESS). The mass with high signal intensity was found in the radius, ulna and ulnar subcutaneous tissue of the distal forearm, and the signal intensity of three lesions were almost same

the pathological lesion was performed under regional anesthesia. A skin incision, which included the fistula, was made on the dorso-ulnar aspect of the wrist. There was a hole in the ulnar aspect of the metaphyseal ulna and the inflammatory synovitis continued to the fistula. The distal ulna was resected at the proximal portion from the hole. The proliferative synovium from the DRUJ and RCJ was extensively removed. There was also a hole in the dorso-ulnar aspect of the distal radius; the synovium from the radius was excised radically through the hole. A surgical specimen was examined microbiologically and histopathologically. Gram, Ziehl-Neelsen, fluorescent, and fungal staining were performed. The formalin-fixed tissues were embedded in paraffin and processed for hematoxylin and eosin and the Ziehl-Neelsen stain. For microbiological examination, aerobic, anaerobic, bacterial, and fungal cultures were done on excised surgical tissues. For culture of the mycobacterium, solid and broth culture systems (Kudo PD culture, Japan BCG Laboratory, Tokyo, Japan, and MGIT, Japan Becton, Dickinson and Company, Tokyo, Japan) were used under 30°C and 37°C. The PCR kit described above was also used.

Histological examination revealed epithelioid granuloma with caseous necrosis, and Ziehl-Neelsen staining showed acid-fast bacilli (Figure 3a and 3b). The PCR result was positive for *M. intracellulare* at one week postoperatively. After the diagnosis was confirmed by the results, the patient received treatment with three anti-tuberculous drugs: rifampicin (450 mg daily), clarithromycin (400 mg daily), and levofloxacin (500 mg daily), as recommended by an infectious disease specialist. Bacterial and fungal cultures were all negative. At one month after the surgery, the wound had healed and the wrist swelling had decreased. Colonies were obtained from the mycobacterial culture at nine weeks after the surgery, and *M. intracellulare* was identified by performing DNA-DNA hybridization (Kyokuto Pharmaceutical Industrial Co., Ltd, Tokyo, Japan). At three months after the surgery, the swelling disappeared; the three anti-tuberculous drugs were continued for one year. No side effects of drugs were experienced. At the last follow-up, 3 years postoperatively, the patient felt no pain and no disability in daily activities and had no recurrence (Figure 4a). The grip strength was 14.3 Kg and 18.2 Kg for the right and left hands, respectively. The range of motion of the right extremity was as follows: wrist dorsal flexion, 35 degrees; wrist palmar flexion, 35 degrees; forearm pronation, 90 degrees; and forearm supination, 90 degrees. Sclerotic changes were observed in the preoperative cystic lesion of the distal radius; no osteolytic changes of the distal ulna were observed on a wrist radiograph (Figure 4b).

DISCUSSION

Mycobacterium intracellulare is one of the NTM species[1]. It causes lung disease, cervical lymphadenitis, and skin, bone and joint infections[1]. In the upper extremity, it is a rare cause of tenosynovitis, and especially of arthritis and osteomyelitis[2-4]. Although disseminated NTM in-

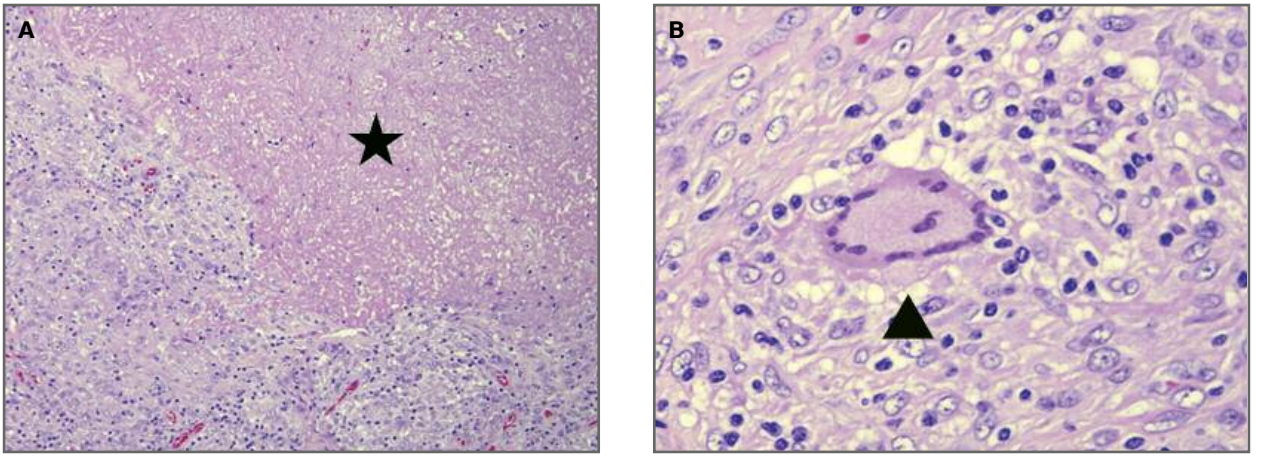

FIGURE 3. Histopathologic photograph. **A**,**B**) Histological sections stained with hematoxylin and eosin show epithelioid granuloma (arrow head) with caseous necrosis (asterisk), infiltration of inflammatory cells, and fibrosis. Langhans giant cells were found, as seen in b (magnification: a, ×100; b, ×400)

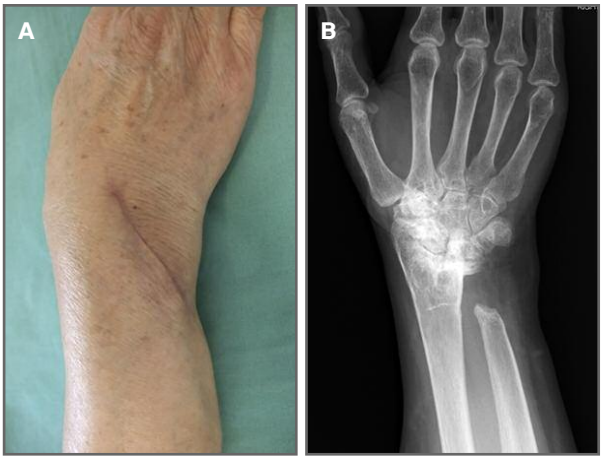

FIGURE 4. Final follow-up appearance and plain radiograph of the right wrist. **A**) Swelling of the right wrist had disappeared at the final follow-up. **B**) Final follow-up plain radiograph of the right wrist showed the change in distal radius from preoperative cystic lesion to sclerosis. No osteolytic change was observed at the resected ulna

fections in immunocompromised patients have received attention recently, there also have been sporadic reports of these infections in immunocompetent patients. The mechanism of musculoskeletal system infection due to NTM has been reported as occurring via hematogenous contamination from surgical treatment or penetrating injury, and steroid injections[2,6]. In this case, a hematogenous spread or a minor trauma associated with the patient's job may be the cause as there was no history of obvious trauma.

To establish a diagnosis of mycobacterium infection, the most reliable method is an open biopsy of the pathological lesion. The surgical specimens should be examined histopathologically without delay. Acid-fast organisms can be confirmed by performing Ziehl-Neelsen and fluorescent stains, and a presumptive diagnosis can be made by observing granuloma formation. The American Thoracic Society recommends the use of two kinds of culture media, solid and broth, at temperatures 35°C and 28°C–32°C, for accurate detection[7]. PCR is useful for early detection of the mycobacterium[8]. A combination of histological examination and PCR results enabled an early diagnosis of *M. intracellulare* infection; the PCR was especially helpful in the identification of the organism and therefore, in the initiation of treatment with anti-tuberculous drugs.

In this case, the patient was diagnosed with rheumatoid arthritis by her previous physician. This misdiagnosis may have been led by the manifestation of the wrist swelling and radiographic findings of the wrist joint. Although radiography revealed wrist bone and joint destruction, her condition did not meet the 2010 rheumatoid arthritis classification criteria[9]. The presentation of an unclosed fistula with discharge made us suspect infection. This case illustrates the fact that NTM infection should always be considered as a possible diagnosis in any patient with chronic swelling[6].

Our treatment was successful in retaining the wrist joint by using a combination of radical surgical debridement and anti-tuberculous drugs. After a surgical reduction of the infectious lesion, anti-tuberculous drugs were administrated for one year with monitoring for recurrence and side effects. As mentioned above, rheumatoid arthritis is not a likely diagnosis in this patient presenting only a wrist monoarthritis. Literature searches were made on the Medline and PubMed. And additional cross-reference checks of the bibliographies were performed. Search terms included mycobacterium, infection, and arthritis/ osteomyelitis. Previous reported cases with arthritis and osteomyelitis of the extremities due to *Mycobacterium avium complex* or *intracellulare* in immunocompetent patients are listed in Table I. A state without immunosuppressive therapy including steroid treatment, human immunodeficiency virus infection, or acquired immune deficiency syndrome, was defined as an immunocompetent condition. Operative resection of the infected tissue appears to be necessary, even if prolonged drug therapy is administered (success rate: without surgery; 0/1, with surgery; 6/6). Although the period of drug therapy after surgical treatment was from 12 to 24 months, the duration seemed to be empirical. The successful result obtained in our case may be due to the good immune status of the host. A compromised immune status has been discussed as a risk factor for recurrence and dissemination of NTM infection. Kozin et al. reported in a series of NTM infections of the upper extremity that 13 of 15 immunocompetent patients had achieved resolution; in contrast, only four of 10 immunocompromised patients achieved resolution[2].

We had also planned an additional surgery, wrist arthrodesis, if the NTM infection was uncontrollable after surgical debridement and medication. Taniguchi et al. reported two cases of infected wrist arthritis treated by using vascularized fibular graft[10]. They performed two-stage procedures, involving debridement of the infected tissue and a vascularized fibular osteocutaneous graft, and achieved resolution of infection.

In summary, excisional biopsy for histological and

TABLE I. PREVIOUSLY REPORTED CASES OF OSTEOMYELITIS AND ARTHRITIS IN THE EXTREMITY CAUSED BY NONTUBERCULOUS MYCOBACTERIA (MYCOBACTERIUM AVIUM COMPLEX, INTRACELLULARE) IN IMMUNOCOMPETENT PATIENTS

Case	Age, gender[a]	Past history[b]	Involved site[c]	Mycobacterium[d]	Trauma	Treatment[f]	Medication[g]	Duration[h]	Outcome
1 [11]	61, M	HT, DM	Wrist	intracellulare	+	A (numerous)	INH, RFP	51	Unresolved
2 [12]	43, M	-	Ankle	MAC	+	EB, A, D, F	AMK (→CAM), RFP, EB, CPFX,	18	Resolved
3 [13]	25, M	gonococcal urethritis	Wrist CLF,	MAC	-	EB, F	AMK, ETH, RFP	NA	Resolved
4 [6]	53, F	VSD	Wrist, MPJ	MAC	Po-VSD[e]	EB, EB, A (R), EB (L)	CAM, EB, RBT	24	Resolved
5 [14]	33, M	AS	Ankle	MAC	-	A, EB	CAM, EB, RBT	NA	NA
6 [15]	81, F	tuberculous pleurisy	Knee	MAC	-	EB	RFP, SM, INH	12	Resolved
7 [16]	27, M	-	Knee, carpal tunnel, sacroiliac joint	Intracellulare	-	A, EB, OCTR + B, B	INH, ETH, EB, PN, RFP	NA	Resolved
8 [17]	74, M	NA	Wrist	MAC	NA	EB	NA	NA	NA
9 current case	67, F	-	Wrist	Intracellulare	-	EB	RFP, CAM, LVFX	12	Resolved

a. M, male; F, female
b. HT, hypertension; DM, diabetes mellitus; VSD, ventricular septal defect; AS, ankylosing spondylitis
c. MPJ, metacarpophalangeal joint
d. MAC, Mycobacterium avium complex
e. Po-VSD, postoperation of VSD
f. A, aspiration; EB, excisional biopsy; D, debridement; F, fusion; OCTR, open carpal tunnel release; B, biopsy
g. INH, isoniazid; CPFX, ciprofloxacin; AMK, amikacin; RFP, rifampicin; EB, ethambutol; CAM, clarithromycin; ETH, ethionamide; CLF, clofazimine; RBT, rifabutin; SM, streptomycin; PN, pyridoxine; PAS, paraaminosalicylic acid; LVFX, levofloxacin
h. Duration of anti-tuberculous drugs (month)
NA, not applicable

microbiological analysis was essential to obtain a definite diagnosis for joint and bone infection due to mycobacterium, and a successful outcome was achieved with a combination of radical surgical debridement and drug therapy. Mycobacterial infection should be included in the differential diagnosis for chronic wrist swelling.

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REFERENCES

1. Shinnick TM, Good RC. Mycobacterial taxonomy. Eur J Clin Microbiol Infect Dis 1994;13:884-901.
2. Kozin SH, Bishop AT. Atypical Mycobacterium infections of the upper extremity. J Hand Surg Am 1994;19:480-487.
3. Hellinger WC, Smilack JD, Greider JL, Jr., et al. Localized soft-tissue infections with Mycobacterium avium/Mycobacterium intracellulare complex in immunocompetent patients: granulomatous tenosynovitis of the hand or wrist. Clin Infect Dis 1995;21:65-69.
4. Zenone T, Boibieux A, Tigaud S, et al. Non-tuberculous mycobacterial tenosynovitis: a review. Scand J Infect Dis 1999;31:221-228.

5. Marchevsky AM, Damsker B, Green S, Tepper S. The clinicopathological spectrum of non-tuberculous mycobacterial osteoarticular infections. J Bone Joint Surg Am 1985;67:925-929.
6. Kanik KS, Greenwald DP. Mycobacterium avium/Mycobacterium intracellulare Complex-Associated Arthritis Masquerading as a Seronegative Rheumatoid Arthritis. J Clin Rheumatol 2000;6:154-157.
7. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. Am Rev Respir Dis 1990;142:940-953.
8. de Charnace G, Delacourt C. Diagnostic techniques in paediatric tuberculosis. Paediatr Respir Rev 2001;2:120-126.
9. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 62:2569-2581.
10. Taniguchi Y, Yoshida M, Doi N, Tamaki K, Tamaki T. Vascularized fibular osteocutaneous grafts in the treatment of severely infected wrist arthritis. J Reconstr Microsurg 2002;18:71-75.
11. Halleran WJ, Martin NL. Nontuberculous mycobacterial arthritis: report of a chronic case. J Kans Med Soc 1982;83:284--286.
12. Jones AR, Bartlett J, McCormack JG. Mycobacterium avium complex (MAC) osteomyelitis and septic arthritis in an immunocompetent host. J Infect 1995;30:59-62.
13. Rolfe B, Sowa DT. Mixed gonococcal and mycobacterial sepsis of the wrist. Clin Orthop Relat Res 1990;100-103.
14. Yang DH, Chang WC, Cheng MF, Lai JH, Chang DM, Chen CH. Peripheral arthritis caused by Mycobacterium avium-intracellulare in a patient with ankylosing spondylitis. J Clin Rheumatol 2009;15:323-324.
15. Tanaka M, Matsui H, Tsuji H. Atypical mycobacterium osteomyelitis of the fibula. Int Orthop 1993;17:48-50.
16. Cheatum DE, Hudman V, Jones SR. Chronic arthritis due to Mycobacterium intracellulare. Sacroiliac, knee, and carpal tunnel involvement in a young man and response to chemotherapy. Arthritis Rheum 1976;19:777-781.
17. Whitaker MD, Jelinek JS, Kransdorf MJ, Moser RP, Jr., Brower AC. Case report 653: Arthritis of the wrist due to Mycobacterium avium-intracellulare. Skeletal Radiol 1991;20:291-293.