

[ CASE REPORT ]

## Tuberculosis of the Wrist Accompanied with Calcium Pyrophosphate

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### Abstract:

This is a rare case of tuberculosis (TB) complicated with pseudogout of the wrist joint in a non-immunocompromised 84-year-old female with a history of pulmonary tuberculosis. She was diagnosed with extrapulmonary tuberculosis of the wrist based on a polymerase chain reaction (PCR) study and synovial fluid aspiration in which the cytology was positive for acid-fast bacilli. Calcium pyrophosphate was also positive. We must be careful not to miss articular tuberculosis as it may mimic common inflammatory arthritis, such as pseudogout of the wrist. Even if the patient is positive for calcium pyrophosphate, this does not exclude the possibility of articular tuberculosis.

**Key words:** tuberculous arthritis, wrist, pseudogout

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### Introduction

Tuberculosis (TB) bacteria can infect any bone, joint, tendon, or bursa. However, the most common musculoskeletal site for infection includes the spine and weight-bearing joints of the hip and knee. TB of the wrist or carpal bones is rare. Moreover, a case of articular tuberculosis concomitant with pseudogout has been reported only once, with this being the second such case report.

### Case Report

A previously healthy 84-year-old Japanese female was admitted to the department of internal medicine at a hospital for acute heart failure due to atrial fibrillation. Before admission, the patient had a three-month history of a spontaneously appearing painful lump on the dorsal area of the right wrist, which had gradually increased in size with no history of trauma. With a concomitant finding of a swollen right wrist, a positive QuantiFERON TB-3G result, and an interferon-gamma concentration of more than 10 IU/mL, the patient was suspected of having *Mycobacterium tuberculosis* (*Mtb*) infection. Ziehl-Neelsen staining of the sputum and

gastric juice was negative for anti-acid bacilli. She was subsequently referred to our hospital after two weeks of therapy for acute heart failure.

On examination, a painful swelling, measuring approximately 4×4 cm with cellulitic inflamed overlying skin, was observed in the dorsal area of the right wrist and hand (Fig. 1). Wrist movements were restrictive and painful. This finding suggested the presence of an active inflammation and abscess. She had constitutional symptoms, including low-grade fever, a 10-kg weight loss over the last six months, fatigue, and anorexia. She had no history of night sweats, cough, or other general diseases, such as kidney disease or diabetes mellitus. The patient had a history of pulmonary tuberculosis when she was 14 years of age, which was treated by injections of streptomycin twice.

A chest X-ray revealed consolidation in the right upper lobe, and a computed tomography (CT) scan revealed previous inflammatory reactions, suggestive of non-active tuberculosis. (Fig. 2), although a CT scan revealed no sign of active pulmonary tuberculosis. An X-ray and a CT scan of the wrist revealed an osteolytic lesion of the carpal bones without findings of calcification (Fig. 3). Non-contrast magnetic resonance imaging (MRI) confirmed the presence of multiple osteolytic lesions that showed extensive soft tissue thick-

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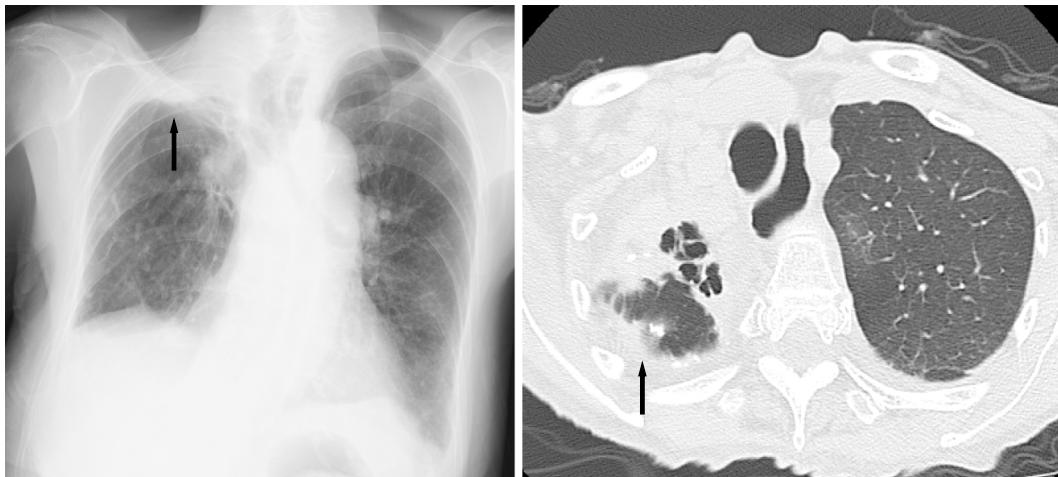
ening, edema of the extensor tendons, and fluid that mainly affected the dorsum of the wrist (Fig. 4). Aspirated synovial fluid was yellow/white in color (Fig. 5), and an examination for calcium pyrophosphate (CPPD) crystals was positive. Ziehl-Neelsen staining was positive for acid-fast bacilli and a polymerase chain reaction (PCR) was also positive for *M.*



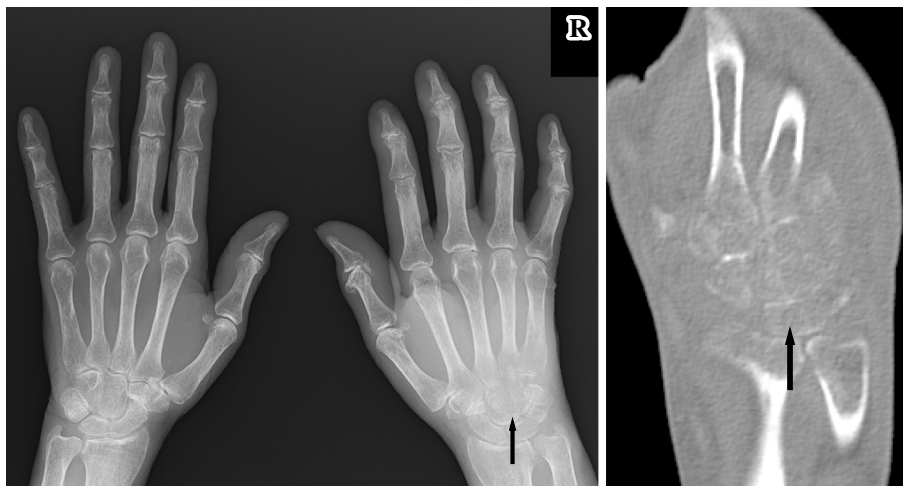
**Figure 1.** Swelling can be observed in the dorsal area of the right wrist and hand measuring approximately 4×4 cm with cellulitic inflamed overlying skin.

*tuberculosis* on the day of consultation. Standard bacterial cultures were negative, and a tubercle bacillus culture was positive for *M. tuberculosis* with a good sensitivity for standard antituberculous drugs (Table). As re-examination of Ziehl-Neelsen staining of the sputum and gastric juice was negative for anti-acid bacilli, PCR of the sputum was also negative.

Other laboratory investigations showed a total leukocyte count of 5,600/ $\mu$ L with neutrophils (76.6%) and lymphocytes (19.0%). Hemoglobin was 8.4 g/dL, albumin was 2.4 g/dL, blood urea nitrogen was 50.0 mg/dL, creatinine was 1.46 mg/dL, calcium was 8.5 mg/dL, the erythrocyte sedimentation rate was over 140 mm in 1 h and over 140 mm in 2 h, IgG-rheumatoid factor (RF) was 1.8 U/mL (normal range: 0-1.9 U/mL), anti-cyclic citrullinated peptide (CCP) antibody was 6.2 U/mL (normal range: 0-4.4 U/mL), antinuclear antibody (ANA) was 160 times (normal range: -39 times) and adenosine deaminase was 259 U/L (normal range: 5-20 U/L). On the second day of admission, extensive drainage and debridement were performed. The day be-

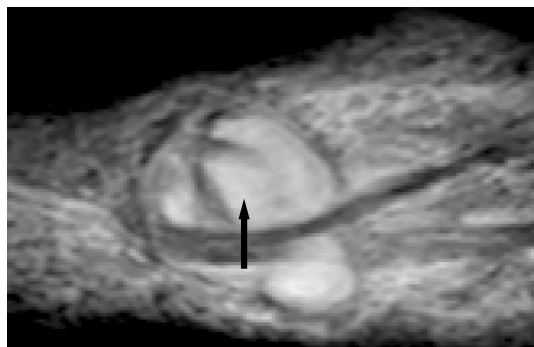


**Figure 2.** A chest X-ray reveals consolidation in the right upper lobe, and a CT scan revealed previous inflammatory reactions, suggestive of non-active tuberculosis.



**Figure 3.** An X-ray and a CT scan of the wrist reveal an osteolytic lesion of the carpal bones without findings of calcification.

fore surgery, a sinus erupted after cheese-like pus was drained spontaneously from the fifth palmar digital crease (Fig. 6). A histological assessment of the synovial membrane showed Langhans-type multinucleate giant cells, comprising multiple nuclei arranged in a horseshoe shape at the periphery surrounded by a lymphocyte infiltration and case-



**Figure 4.** Non-contrast MRI T2-weighted image confirms the presence of multiple osteolytic lesions and shows extensive soft tissue thickening, edema of the extensor tendons, and fluid that mainly affected the dorsum of the wrist.

ous necrosis, which are common findings in TB granuloma (Fig. 7). She was diagnosed as having extrapulmonary tuberculosis affecting the distal radius and carpal bones with tuberculous tenosynovitis. Her treatment for TB involved three drugs: isoniazid (5 mg/kg/day); rifampicin (10 mg/kg/day); and ethambutol (25 mg/kg/day) was started on the first day of admission for two months. *M. tuberculosis* was identified on 4th week by one of the three sputum culture bottles. Then, a combination treatment of isoniazid (5 mg/kg/day) and rifampicin (10 mg/kg/day) was prescribed, which is the



**Figure 5.** Aspirated yellow/white synovial fluid.

**Table.** Laboratory Data.

Interferon-Gamma release assay (IGRA)					
QuantiFERON TB-3G		>10 IU/mL			
Acid-fast bacilli in sputum					
Day 1	smear negative	PCR of TB (-)	culture (+) identified as <i>M. tuberculosis</i> on 4th week		
Day 2	smear negative		culture (-)		
Day 3	smear negative		culture (-)		
Acid-fast bacilli in gastric juice					
Day 1	smear negative		culture (-)		
Acid-fast bacilli in aspiration fluid of wrist					
Day 1	smear 1+ weakly positive	PCR of TB (+)	culture (+) identified as <i>M. tuberculosis</i> on 3rd week		
Test for drug sensitivity (aspiration fluid in the wrist)					
Drug	Result	Drug	Result	Drug	Result
SM 10.0	S	EB 2.5	S	CS 30	S
INH 0.2	S	KM 20.0	S	PAS 0.5	S
INH 1.0	S	EVM 20	S	LVFX 1.0	S
RFP 40.0	S	TH 20	S	PZA 100	S
SM: streptomycin, INH: isoniazid, RFP: rifampicin, EB: ethambutol, KM: kanamycin, EVM: enviomycin, TH: ethionamide, CS: cycloserine, PAS: para-amino-salicylic-acid, LVFX: levofloxacin, PZA: pyrazinamide					
Crystals in aspiration fluid of wrist					
Urate crystals (-)			Pyrophosphate crystals (+)		
IGRA: interferon-gamma releasing assay, PCR: polymerase chain reaction, TB: tuberculosis					

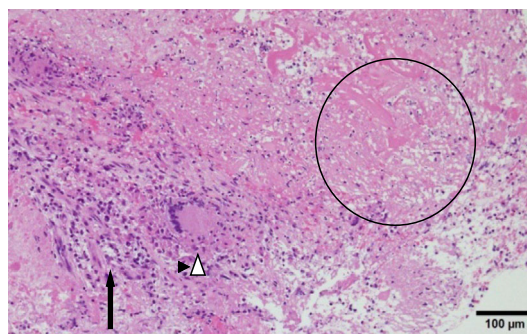


**Figure 6.** The day before the surgery, a sinus erupted and cheese-like pus drained spontaneously from the fifth palmar digital crease.



**Figure 8.** Drug therapy allowed a recovery of swelling and pain after six months of follow-up.

standard treatment for patients over 80 years of age in Japan. Although it was once followed by rifampicin (10 mg/kg/day) due to neutropenia identified at the three-month medical follow-up, sensitization therapy for isoniazid was successful and the two-drug therapy was continued. This combination therapy for 6 months allowed recovery from swelling and pain (Fig. 8), and the sinus of the fifth digit was soon closed after drug therapy. At the beginning of the therapy non-steroidal anti-inflammatory drugs (NSAIDs) were administered as a therapy for pseudogout of the wrist until pain was relieved. After the 4-month follow-up, laboratory investigations showed the erythrocyte sedimentation rate was 120 mm in 1 h and over 140 mm in 2 h. Moreover, the patient complained of functional disability of the right wrist despite starting occupational physiotherapy soon after surgery. Her disabilities of the arm, shoulder, and hand in terms of the Japanese Society for Surgery of the Hand version of the Disability of Arm, Shoulder, and Hand (DASH-JSSH) questionnaire (1) despite continued occupational physiotherapy were 70.8/100 on discharge from our hospital and 69.8/100 at the six-month follow-up. Unfortunately, 7 months after her first consultation to our hospital, she died because of type A influenza infection accompanied by pneumonia.



**Figure 7.** Histological assessment of synovial membrane shows Langhans-type multinucleate giant cell (arrow head), comprising multiple nuclei arranged in a horseshoe shape at the periphery surrounded by lymphocyte infiltration (arrow) and caseous necrosis (circle), which are common findings in TB granuloma.

## Discussion

Skeletal tuberculosis occurs in 10% of all patients with tuberculosis (2). The major areas of predilection are, in decreasing order of frequency, the spine, hip, knee, foot, elbow, hand, shoulder, bursal sheaths, and other sites (3). Wrist osteoarticular TB is uncommon, accounting for 1% of all skeletal TB cases (4). The incidence of extrapulmonary TB has been rising due to the increasing number of immunosuppressed patients (5, 6). As for the distribution of tuberculous infection of the wrist, the dominant reportedly has a higher prevalence of involvement (7), as it was in this case. A case of tuberculosis of a hand concomitant with pseudogout has been reported (8), and this is the second case report. The mechanism of articular tuberculosis is suspected to be direct inoculation from the adjacent bone or joint infection or seeding from a tuberculous lesion in the pleuropulmonary or genitourinary system (9). TB of the peripheral joints and tendons occurs infrequently, but if it remains untreated, it can cause serious joint and tendon destruction as well as a spread of the infection to the surrounding bursa, muscle, and other soft tissues (7). Conversely, it was reported that a tuberculous infection of the wrist originated from the tenosynovium and then extended to the joint or bone (10, 11). Concomitant crystal and infectious arthritis is rare as bacterial infection presents in only 1.5% of joint aspirates containing crystals (12). As already mentioned, articular tuberculosis concomitant with pseudogout has not been reported, except for the one case wherein it occurred in 3rd metacarpal joint (8). Unlike for gout, there are no known serum biochemical markers for pseudogout. Most cases of pseudogout are associated with ageing, trauma, hyperparathyroidism, Gitelman syndrome, and haemochromatosis (13). In this case, in addition to mild chronic kidney disease, the recent acute heart failure, malnutrition, and hypoalbuminemia may have caused CPPD deposition.

The initial symptoms are nonspecific in the form of joint pain, swelling, effusion, stiffness, carpal tunnel syndrome, movement limitation, and discharging sinuses. Sclerosis and osteolytic lesions, the main radiographic features of bony TB, are nonspecific and are present in other conditions, such as inflammatory arthritis, pyogenic osteomyelitis, and some malignancies (14). CT and MRI scans, although nonspecific, may help in differential diagnosis and evaluation of the extent of the lesion. The diagnosis can be easily delayed or missed because it manifests nonspecific clinical signs, and we first tend to suggest numerous other disease entities, such as pseudogout, pyogenic arthritis, or rheumatoid arthritis. In this case, a positive CCP test and ANA should be interpreted with care. We recognize these data form the basis for the diagnosis of TB infection. Patients with TB frequently produce anti-citrullinated protein antibodies, most frequently detected by a CCP test. Increased levels of anti-CCP2 have been reported in up to 32% of patients with TB (15). These patients also displayed an increased frequency of other autoantibodies such as RF and ANAs (16). Based on the 2010 ACR/European League against Rheumatism (ACR/EULAR) classification criteria, it was indicated as definitive RA; however it was unable to be excluded, activity of RA was considered to be not as high relative to the IgG-RF value. We administered no specific therapy against RA. The time before a confirmed diagnosis of TB in this case was one month. In the literature, the mean time to diagnosis is reportedly  $6.5 \pm 2.5$  months (range: 3-12 months) (17-19). Although wrist tuberculosis is rare, it should be the first and foremost differential diagnosis in the presence of atypical clinical and radiological features of a carpal lesion, particularly in a patient with a medical history of TB therapy. In the present case, as there were no signs of a so-called cold abscess, acute infective etiology like pseudogout or rheumatic arthritis was considered as a differential diagnosis. It was likely that the acute arthritis was caused by the pseudogout crystals. Diagnosis is often established after direct microscopic examinations, a PCR assay for *M. tuberculosis*, and a Mycobacterium culture from cold abscess aspiration fluid. If these examinations are negative, a surgical biopsy is recommended. PCR is particularly useful as it is a molecular biologic technique that uses nucleic acid amplification, is highly sensitive for detecting *M. tuberculosis*, and takes only few hours for confirmation. Treatment success depends on the appropriate combination therapy of drug(s) and debridement. It is recommended that the treatment should continue for a minimum of 12 months if there is osteoarticular involvement (20). There are reported cases of hand tuberculosis with antitubercular chemotherapy using four drugs [isoniazid (INH), rifampin, pyrazinamide, and ethambutol] for 4 months, followed by three drugs (INH, rifampin, and pyrazinamide) for 3 months, and finally two drugs (INH and rifampin) for 11 months (21). However, the optimal duration of treatment has been an issue of considerable debate. In our case, the delay in admission to a medical institution was suspected to be the major reason for her dis-

ability in the right upper extremity. As a consequence of the diagnostic delay, despite a combination therapy of drugs and extensive drainage and debridement followed by early physiotherapy, the motor function remained unchanged at the latest six-month follow-up.

### Conclusion

This case highlights that TB should be considered when dealing with nonspecific chronic wrist arthritis, particularly if the patient has a history of old tuberculosis. In addition, even if examination for crystals reveals calcium pyrophosphate, tuberculosis of articulation cannot be denied. In conclusion, carpal tuberculosis is rare, but it should be the first considered diagnosis in the presence of a clinical history of *M. tuberculosis* and radiological features of a carpal lesion.

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

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