Cureus
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Open Access Case Report

Diagnostic Challenges of Wrist Tuberculosis Without Pulmonary Involvement in a Non-endemic Area: A Case Report

Review began 07/22/2026
Review ended 10/11/2026
Published 10/22/2026

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DOI: 10.7759/cureus.118396

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Abstract

Tuberculosis is a systemic infection caused by the *Mycobacterium tuberculosis* complex bacilli. Musculoskeletal tuberculosis of the wrist is rare among extrapulmonary tuberculosis and usually develops from hematogenous spread of reactivated pulmonary tuberculosis or from direct inoculation of bacilli into the tissues of the hand. Hand and wrist tuberculosis treatment consists of a pharmacologic regimen, surgery, or a combined treatment. We present a highly atypical case of an elderly man who was diagnosed with tuberculosis of the right wrist, with a delayed onset, a progressive and recalcitrant course, and, more importantly, without a pulmonary infection. Our patient underwent two surgical debridements in order to achieve an eventual diagnosis. The lack of pulmonary infection obscured the diagnostic procedure, which was initially directed at common bacterial pathogens. This delay in diagnosis led to severe bone and soft tissue involvement with extensive resorption of the carpal bones. Tissue biopsy and cultures are imperative for the diagnosis and antibiotic-guided treatment. A combined approach of surgical and antibiotic chemotherapy is preferred to optimize patient outcomes. A high index of suspicion is therefore imperative in the setting of a recalcitrant and progressive inflammatory arthropathy of the wrist joint, even without pulmonary involvement, and even in regions with declining tuberculosis infection rates.

Categories: Orthopedics, Infectious Disease
Keywords: hand infection, mycobacterium tuberculosis complex, osteomyelitis, tuberculosis, wrist infection

Introduction

Tuberculosis (TB) is an infectious disease caused by the *Mycobacterium tuberculosis* complex bacilli (Gram-positive). Worldwide, an estimated total of 10.6 million people were diseased with TB in 2022. Most TB cases in 2022 were in Southeast Asia (46%) and Africa (23%), but there were smaller shares in the Eastern Mediterranean region (8.1%) [1]. Extrapulmonary TB (EPTB) can involve virtually any site in the human body; most commonly, this includes lymph nodes (35%). Bone and joint involvement accounts for 10-15% of all EPTB cases [2]. Musculoskeletal TB usually results from bloodstream dissemination of reactivated lung disease or direct inoculation of bacilli in the tissues of the hand in particular [3,4]. The infection may involve various soft tissue structures, bones, or joints. Treatment of TB in the hand and wrist consists of non-surgical, surgical, or combined treatment [5]. These are rare cases associated often with subtle initial symptoms and a protracted clinical course, leading to delays in diagnosis and treatment and oftentimes to severe joint compromise and deformity, substantially impacting patient quality of life.

We present the case of an elderly man who was diagnosed with TB of the right wrist, with delayed onset in a low-incidence area and without pulmonary involvement.

Case Presentation

An elderly (94-year-old) male patient presented in the orthopedic department of our hospital (regional hospital - level III trauma center) in June 2023 with wrist joint pain, swelling, and tenderness in his right hand that had worsened in the period of the previous nine months. The swelling was located on the volar and the dorsal side. Since October 2022, when the patient underwent the initial wrist radiograph (Figure *1*), he had visited various other orthopedic surgeons for consultation. He underwent one intraarticular corticosteroid injection in December 2022 and one in February 2023 at different institutions. Past history includes a minor wrist injury seven decades before and was operated on for carpal tunnel syndrome in his right hand in 1988. The patient mentioned that he had minor wrist complaints for years, but no official diagnosis had been made. There was no history of TB or having contact with a TB patient. Past medical history included atrial fibrillation, osteoporosis, and prostate hyperplasia under treatment.

How to cite this article
Athanasopoulou M, Kolovos I, Pavlaki M, et al. (October 22, 2026) Diagnostic Challenges of Wrist Tuberculosis Without Pulmonary Involvement in a Non-endemic Area: A Case Report. Cureus 18(10): e118396. DOI 10.7759/cureus.118396

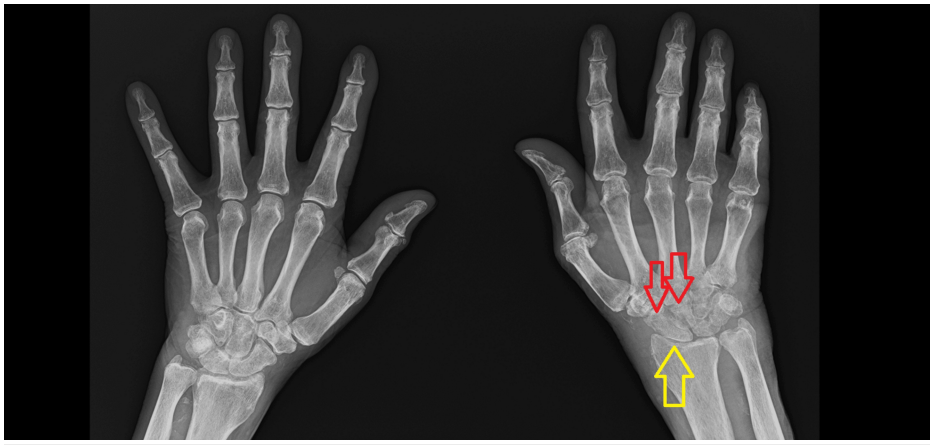


FIGURE 1: Plain radiograph of the patient's hands in October 2022

The yellow arrow indicates joint line narrowing, and the red arrows showcase a mild osteopenic appearance of carpal bones.

Clinical examination showed joint deformation, excessive swelling, and the existence of a sinus tract with exudation of purulent (caseated-like) fluid. There was no presentation of systemic symptoms or fever. When new X-rays were performed at presentation, they revealed worsened radiocarpal arthritis and subtle osseous involvement with a bone osteoporotic appearance of the carpal bones.

An MRI with IV contrast agent was ordered, which showed significant soft tissue involvement and joint effusion (Figure *2*). The patient was initially scheduled for a limited local debridement to acquire tissue samples for culture and guide antibiotic treatment and received standard perioperative antibiotic coverage after the samples had been taken (cefoxitin 2 g TID). Gram and Ziehl-Neelsen stains were negative. The patient's clinical course had not improved substantially, and, therefore, a CT of the right hand was obtained in August 2023. The scan showed widespread carpal bone involvement with multiple sites of bone resorption (Figure *3*).

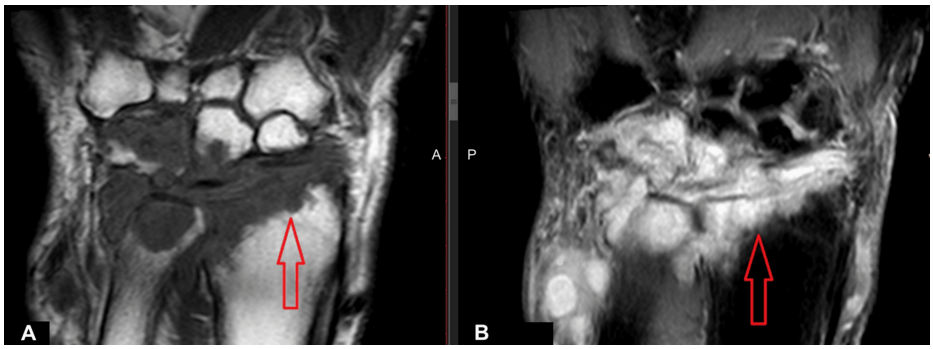


FIGURE 2: MRI of the right wrist showing joint effusion and severe bone and synovial involvement

T1 (A) and T2 (B) coronal views of the wrist. The red arrows show areas of osseous and soft tissue involvement, namely, low signal in T1 and high signal in PD sequences. The asterisk showcases a possible abscess in the subcutaneous tissue adjacent to the ulna.

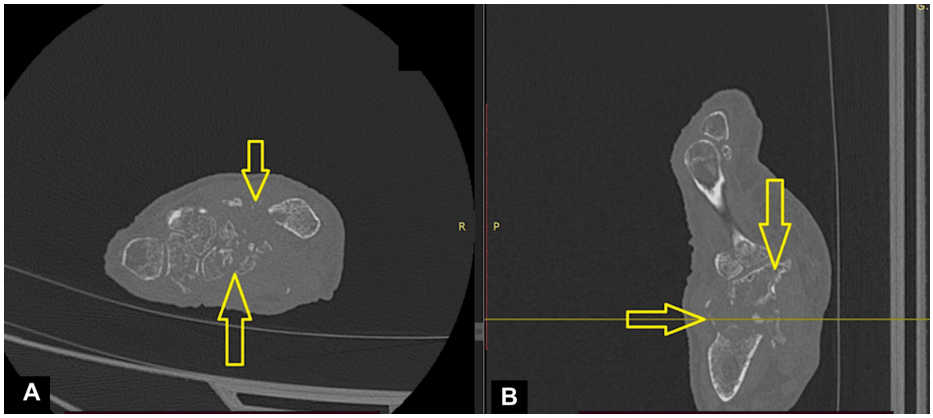


FIGURE 3: CT scan of the right wrist

Axial (A) and sagittal (B) views of the wrist CT. The yellow arrows indicate osseous destruction.

An incisional biopsy was performed at this timepoint. Caseous necrotic material was intraoperatively recognized. Tissue and bone samples were obtained, and cultures for common microbes, as well as *Mycobacterium*, were sent; a synovial debridement took place, and the joint was washed thoroughly. Molecular testing DNA MTBC PCR (XPERT) diagnosed *M. tuberculosis* within the day and did not detect a drug-resistant strain. The tissue sample cultures in Löwenstein-Jensen medium were positive for a sensitive strain of *M. tuberculosis* approximately three weeks later (Table *1*).

Drug µg/ml	Sensitive	Resistant
Conventional method Lowenstein-Jensen medium		
SM 5.0	X	
SM 10.0	X	
INH 0.2	X	
INH 1.0	X	
EMB 2.0	X	
EMB 4.0	X	
RIF 20.0	X	
RIF 40.0	X	
MGIT		
PZA 100	X	
Molecular sensitivity method (DNA MTBC PCR XPERT)		
INH	X	
RIF	X	

TABLE 1: Antibiotic sensitivity testing for the isolated M. tuberculosis strain

SM: Streptomycin; INH: Isoniazid; EMB: Ethambutol; RIF: Rifampin; MGIT: Mycobacteria Growth Indicator Tube; PZA: Pyrazinamide; MTBC: *Mycobacterium tuberculosis* complex

Pharmacologic treatment was commenced upon PCR confirmation with the standard antibiotic regimen of rifampicin, ethambutol, pyrazinamide, and isoniazid for an IP of eight weeks and a continuation phase with isoniazid and rifampicin of 16 weeks. As the conventional cultures provided the sensitivity results three weeks later, the standard regimen was continued.

A radiograph at that time point showed extensive bone resorption (Figure 4). The patient was referred to a special infectious disease center for TB, where he was subjected to testing for systemic disease, which was negative. Treatment was continued at that institution. Subsequent HIV screening was negative.

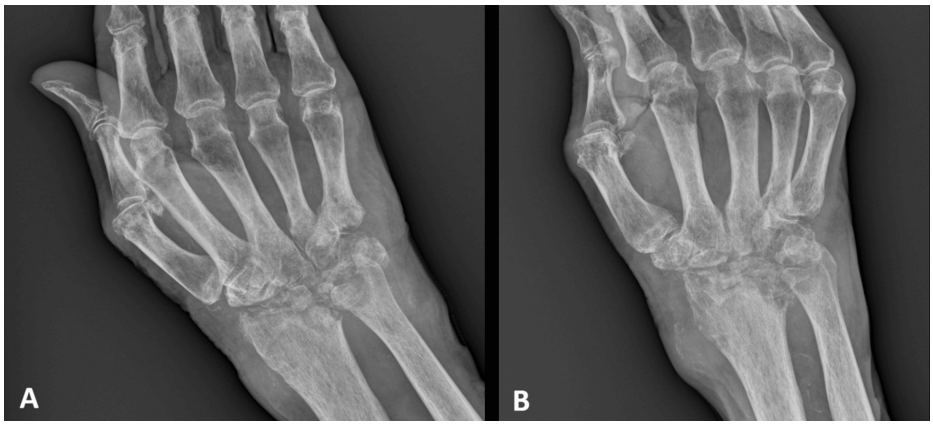


FIGURE 4: Compared to the previous X-rays, there was worsening bone involvement

Right wrist face (A) and oblique (B) radiographs showing extensive osseous destruction and deformity, with areas of resorption (radiolucent areas).

The patient had prompt improvement in his symptoms, and the swelling and tenderness have disappeared over the days following antituberculous treatment initiation. He has regained adequate wrist functionality and is responding well to the treatment. His QuickDASH score after the treatment was 14, a great improvement from his pre-treatment score, which was 65.

Discussion

Mycobacterium is a genus of Gram-positive bacilli. Furthermore, they are non-motile obligate aerobes and do not form spores. Their cell wall consists of lipoarabinomannan and mycolic acids. This cell wall makes it impossible to stain with the regular Gram stain, thereby necessitating the use of the Ziehl-Neelsen stain for diagnosis. It also reduces the penetration of antibiotics into the cells [6].

TB is an infectious disease caused by the *M. tuberculosis* complex, which is made up of the bacterial species *M. tuberculosis*, *M. africanum*, and *M. bovis* [7]. Infection occurs when droplet nuclei containing *M. tuberculosis* bacilli (MTB) from infectious patients reach the respiratory system and then undergo hematogenous and lymphatic dissemination, involving the hilar and mediastinal lymph nodes. Eventually, bacilli enter the bloodstream and reach various organs. Thus, we have pulmonary TB and, through lympho-hematogenous dissemination, EPTB, with possible dormant foci reactivation [8,9]. Bone and joint involvement accounts for 10-15% of EPTB sites [2]. Wrist localization remains rare, accounting for only 2-4% of all affected musculoskeletal sites [10]. On the other hand, direct inoculation of tissues after interruption of the skin integrity has also been described in the literature as the result of needle stick injuries [11], IM injections [12], penetrating trauma [13], or blunt trauma [14], sometimes with delayed presentation. These cases mainly involve cutaneous TB; however, deeper tissues may also be involved. The initial absence of skin lesions in our patient makes this method of contagion less likely, making a reactivation of a hematogenous-spread site in the wrist the most likely scenario. Furthermore, this low-grade infectious procedure may have been aggravated by the steroid injections that were performed.

Hand and wrist infection is usually the result of hematogenous or lymphatic dissemination or direct tissue inoculation [3]. About 12.5% of patients with wrist TB have a history of a pulmonary infection [15]; however, there is often a lack of concurrent pulmonary disease [4]. EPTB is frequent among immunocompromised patients, which is significant considering the resurgence of TB cases with the HIV epidemic [15]. The infection may involve various bony and soft tissue anatomical structures and presentation varies greatly depending on the host's immune status and cell-mediated response. Patients may present with pain, wrist swelling (either palmar or dorsal), joint effusion, stiffness, digital swelling [16], or a discharging wound or sinus in more longstanding cases. Axillary or epitrochlear lymphadenopathy may appear [17]. It is important to note that these findings are not always present and vary depending on which specific tissues of the hand are infected. Wrist involvement, with periarticular swelling and chronic pain, may mimic rheumatologic disease and therefore lead to misdiagnosis [18,19], while there may be a considerable period of time from the initial subtle symptoms until patient presentation [20]. Constitutional symptoms, such as low-grade fever, night sweats, weight loss, and anorexia, can be present. These were not present in our patient, obscuring the diagnostic procedure, potentially indicating an isolated non-infectious wrist localization. Our patient

presented with a subacute progressive form of wrist arthropathy, which eventually developed a draining sinus and deteriorating hand function.

The characteristic granulomatous inflammatory reaction against the MTB is called a tubercle, which can eventually progress to a macroscopically visible granuloma. The latter contains MTB bacilli within macrophages, fibrin-rich exudate, lymphocytes, and multinucleated giant cells in the fibroblastic rim. They can be caseating and non-caseating [21]. Diagnosis of musculoskeletal TB is established with a positive culture or pathoanatomy examination from joint aspirate or tissue biopsy [22] when the *Mycobacterium* bacilli are found with smear microscopy using the Ziehl-Nielsen stain. The gold standard method is a culture for *M. tuberculosis* and a drug sensitivity test. There exist two immunological methods for diagnosing the disease, the tuberculin skin test and the Quantiferon test. There also exist some molecular methods (LAMP, LPA, PCR) [23]. Regarding puncture biopsy in bone and joint TB, low bacterial counts in biopsy samples, atypical locations, and small sample sizes are associated with difficulties in definitive diagnosis via microbiologic cultures and pathoanatomy examination [24]. False negatives, with some studies reporting up to a 50% false negative rate, may hinder timely recognition of the pathogen [18]; such an instance happened to be the case after the first debridement of our patient. Musculoskeletal TB is associated with delays in diagnosis and treatment, potentially leading to adverse outcomes with the need for further operative interventions [25]. This has been established by a number of similar reports. Wang et al. reported on a patient with isolated TB osteomyelitis of the wrist, who underwent two operative biopsy procedures in order to establish the diagnosis before finally commencing pharmacologic treatment [26].

The initial diagnostic approach for a patient with a suspected atypical infection of the hand includes laboratory studies, imaging, and immunological tests. Either incisional or excisional biopsy may be imperative for diagnosis and the sensitivity investigation of the bacilli. There are a lot of case reports and studies showing the delay, sometimes for years, between the presentation of symptoms and the diagnosis of the disease. It is important to recognize the symptoms and send cultures and biopsies of any suspicious tissues that are found, as early diagnosis and treatment can greatly improve the outcome of these patients [27-31]. The extensive bone loss and clinical deterioration of our patient was a result of this delayed clinical course; this diagnosis evaded many clinicians and is not infrequent with similar cases in literature [32].

Radiological investigations are also useful to diagnose wrist TB. In plain radiographs, there may be subtle signs such as the osteopenic appearance of the bones, soft tissue swelling, and, in more advanced cases, bone destruction and joint-line effacement [15]. CT with IV contrast is rarely necessary for diagnosis but may have a role in better detecting sequestrum and draining sinuses [15]. Finally, for early wrist TB not visible on plain radiographs, MRI may be the best imaging modality to depict the extent of soft tissue and bone involvement [20]. These include tenosynovitis (high signal T1), abscess (low T1 and high T2/PD signal), bone destruction (low T1 signal), and rice bodies [20]. In our patient, apart from rice bodies, the initial subtle findings on the radiographs, along with the diffuse bone involvement on the MRI before eventually evident osseous destruction, are indicative of wrist TB.

The disease can be classified by the involvement of different tissues in cutaneous disease, tenosynovitis, bursitis, TB arthritis, osteomyelitis, TB hypersensitivity, and aseptic arthritis in patients with pulmonary TB [33].

The most common presentation is with tenosynovitis of flexor tendons [34]. The dominant hand is affected more often [35]. A rare manifestation of TB disease of the synovium of the long flexor tendons is the compound palmar ganglion [36], occasionally leading to carpal tunnel syndrome [5]. Cutaneous disease is rare and has various clinical manifestations, such as dactylitis and ungual TB. TB bursitis is uncommon. The subdeltoid bursa is the anatomic site most frequently affected, followed by the olecranon bursa. Most commonly, the presenting symptom involves a slowly growing mass; surgical exploration findings include inflammatory exudate and rice bodies within the bursa [37].

TB arthritis of the upper limb is relatively uncommon. In the hand, the phalanges, metacarpals, and associated joints are primarily affected, either solely or in multiple sites; the wrist joint may also be involved. There are five stages of TB arthritis. Stage I, or the synovitis stage, presents with soft tissue swelling. Stage II is early arthritic changes with marginal erosions. Stage III is advanced arthritis with subperichondrial cysts and joint space narrowing. Stage IV includes advanced degenerative joint disease with loss of joint anatomy and function expected after treatment. Finally, stage V is characterized by joint ankylosis [38,39]. The disseminated type is seen in immunocompromised patients, while the bony lesions may involve various bones, including bilateral hand involvement [22]. Septic arthritis of the wrist and carpal osteomyelitis with extensive bone destruction were the infection result in our patient.

Treatment of TB is focused on both curing the patient and minimizing the transmission of the disease. WHO guidelines recommend an initial two-month phase of isoniazid (INH) and rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB), followed by four months of INH and RIF, with doses similar to pulmonary TB. In cases of osteoarticular TB or immunocompromise, the overall regimen duration may be extended, reaching 12 months in total [40]. This drug selection is the mainstay of treatment unless there is known or suspected resistance to any of the first-line drugs. Drug-resistant cases are treated with an IP of 6-9 months

with kanamycin, levofloxacin, ethionamide, cycloserine, pyrazinamide, ethambutol, and isoniazid, followed by 18 months of a continuation phase with levofloxacin, ethionamide, cycloserine, ethambutol, and isoniazid. Bedaquiline is a newer drug used in drug-resistant cases [41]. Our patient received the recommended first-line treatment for EPTB as stated by the WHO guidelines.

Treatment of TB in the hand and wrist consists of pharmacologic, surgical, or combined treatment. In general, non-operative treatment with the standard antibiotic regimen may be the preferred treatment, with surgery performed in select cases [42]. If there is no response with antibiotic treatment alone, patients can undergo surgical debridement [42]. The combination of surgical debridement and antibiotic treatment has been found by many investigators to reduce the chance of recurrence [43]. Other absolute surgical indications are the existence of abscesses and sinuses, median nerve entrapment, and failure of antibiotic treatment [4]. Operative options include drainage, necrotic tissue debridement, synovectomy, tenosynovectomy, and arthrodesis [44,45].

Taking all the above into consideration, the key learning point of the article is to keep a high index of suspicion in select subacute-treatment refractory inflammatory arthropathies, even in areas with a declining rate of TB infection [46]. Our patient had progressive wrist symptoms for a significant period of time that were managed conservatively even though there was no clinical improvement; the diagnosis evaded several physicians. In this context, early use of advanced imaging may facilitate the diagnosis. Moreover, corticosteroid injections in the area may have exacerbated the infectious process until a sinus was formed and the patient presented at our institution. There, an initial limited washout to obtain cultures was done for a presumed infection with common bacterial pathogens, which proved fruitless and created a diagnostic problem while the clinical course of the patient deteriorated with eventual osteomyelitis and bone loss. Therefore, in this setting, it is important to include this atypical pathogen in the differential diagnosis in the absence of clinical response to common treatments and protracted disease courses in order to prevent adverse outcomes. A correct diagnosis eventually laid the groundwork for the definitive treatment, which will likely require further operative measures.

Conclusions

It is evident from our case that the onset of osteoarticular TB of the wrist and its progression are insidious, and the medical history is not always helpful. Care has to be taken to recognize the symptoms and the characteristic clinical appearance of caseated material, which can guide the correct diagnostic approach. Early use of advanced imaging may be warranted in these cases. This highly unusual case report serves as a reminder to include TB in the diagnostic approach of select atypical persistent inflammatory arthropathy of the wrist joint even in the absence of systemic or pulmonary clinical manifestations and in regions where TB cases may be infrequent.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Critical review of the manuscript for important intellectual content: Ioannis G. Spyrou, Panayiotis K. Karampinas, Evangelos Sakellariou, Ioannis Kolovos, Marina Athanasopoulou, Maria Pavlaki, Christina Delavinia, Vasiliki Giannou

Supervision: Panayiotis K. Karampinas

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the

submitted work.

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