Case report

Difficulty in diagnosis and management of musculoskeletal nontuberculous mycobacterial infections

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A 92-year-old male with diabetes mellitus, hypertension, and hyperlipidemia presented with chronic left wrist pain and swelling. Four years prior, he was treated for native left elbow septic arthritis with Methicillin-resistant Staphylococcus aureus, following a penetrating injury with a shard of wood. He received incision, debridement, and intravenous vancomycin with complete resolution.

Two years later, the patient fell and developed left wrist pain and swelling. Symptoms persisted, and he underwent debridement twice with inflammatory mass excision from the left radial wrist. Histopathology revealed necrotizing granulomata. Bacterial and Acid-Fast Bacilli (AFB) cultures were negative. Initially he improved, but over the course of several months, his symptoms worsened, and range of motion became limited. Magnetic resonance imaging (MRI) one year later showed extensive synovitis and joint destruction throughout the wrist.

On presentation to our clinic, the patient denied fever, chills, night sweats, or other systemic symptoms. Vital signs were normal. The left wrist displayed circumferential joint swelling. The volar side of the wrist exhibited significant tenderness and limited range of motion. No drainage, erythema, warmth, or signs of acute infection were observed.

Laboratory evaluation demonstrated a normal complete blood count (CBC) and comprehensive metabolic panel (CMP). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were normal. Incision and debridement were performed. Left wrist capsulotomy revealed a herniating mass of inflamed synovial tissue with caseous exudate (Fig. 1). Synovial tissue histopathology showed acute and chronic inflammation with fibrosis. Bacterial, mycobacterial, and fungal stains were negative. Broad range polymerase chain reaction testing was negative for bacterial, mycobacterial, and fungal DNA.

Four weeks post-operatively, two AFB colonies grew, which were identified as Mycobacterium avium complex (MAC). Daily azithromycin, ethambutol, and rifampin were started. Treatment duration was planned for nine to twelve months, with a wrist fusion planned thereafter. Unfortunately, the patient developed nausea, confusion, and insomnia and self-discontinued therapy. At three-month follow up after therapy termination, the patient’s symptoms were persistent though somewhat improved. After discussion of other pharmacologic options, he declined further antimicrobial or surgical therapy and opted for observation alone.

This case highlights the difficulty in diagnostics with MAC joint infection, which may lead to multiple operative interventions and an inability to tolerate antimycobacterial therapy, resulting in long-term morbidity for the patient.

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ABSTRACT

We describe two cases of musculoskeletal nontuberculous mycobacterial (NTM) infection resulting in undesirable outcomes. These organisms can be difficult to identify and treat, potentially leading to significant morbidity. NTM should remain on the differential for culture negative bone and joint infections, especially with a prior surgical history or environmentally-acquired injuries.
Case 2

A 63-year-old female with hypertension, obesity, and a remote history of bilateral total knee arthroplasty (TKA) presented with chronic right knee pain. She previously required right TKA explant with dynamic spacer placement three years prior to presentation due to joint failure. These operative cultures were negative.

Physical examination revealed a small area of swelling over the medial right knee without erythema or warmth. There was mild pain with range of motion and weight-bearing. Vital signs were normal. An ultrasound-guided aspiration of the right knee yielded sanguinopurulent fluid. Fluid analysis showed 98,721 white blood cells per microliter (98 % neutrophils and 2 % monocytes), 168,000 red blood cells per microliter, and no crystals.

CBC and CMP were unremarkable. ESR was elevated at greater than 130 millimeters per hour. CRP was elevated at 9.51 milligrams per deciliter.

The patient underwent irrigation, debridement, and dynamic spacer explant with placement of a new static antibiotic spacer and knee-spanning intramedullary nail. Multiple synovial fluid and operative tissue cultures grew an AFB on post-operative day five. She was empirically started on amikacin, cefoxitin, and minocycline for coverage of rapidly growing NTM. The isolate was identified as *Mycobacterium abscessus* with an erythromycin resistance methylase (erm) gene detected. Based on limited susceptibility, amikacin, omadacycline, and clofazimine were planned for nine months. Amikacin was stopped due to ototoxicity. Ultimately, she required an above-knee amputation of her right lower extremity due to persistence of pain and inability to tolerate antimycobacterial regime.

This case highlights the prolonged duration of illness and indolence due to NTM periprosthetic joint infections (PJI). Furthermore, it demonstrates the multi-drug resistant nature of *M. abscessus*, difficulty in tolerating therapy, and ultimate morbidity requiring amputation despite prosthetic explantation.

Discussion

Nontuberculous mycobacteria are opportunistic pathogens that are highly ubiquitous in the natural environment [1,2]. There are approximately 200 species of NTM, and 95 % of these are non-pathogenic [2]. Annual prevalence of NTM infection is increasing, currently estimated to be between 2.6 % and 10 %, mostly comprised of pulmonary infections [1].

Despite the environmentally pervasive nature of NTM, infection is relatively uncommon. NTM may cause (i) isolated lung disease, (ii) skin, soft tissue, and orthopedic infections, and (iii) extrapulmonary visceral/disseminated infections [3]. Pulmonary disease is by far the most common presentation; however, NTM infections are phenotypically diverse.

![Fig. 1. Mycobacterium avium complex (MAC) infection of left wrist. (A) Pre-operative findings of circumferential left wrist swelling. (B) Intra-operative findings of caseous exudate and synovial inflammation. (C) MRI with pan-carpal erosions, inflammation, and extensive synovitis. (D) Six months post-operative findings, improvement but persistence of swelling off therapy.](image-url)
and can affect almost every organ system [2]. Isolated pulmonary disease is often seen in immunocompetent hosts with preexisting structural lung diseases [1, 3]. Skin and soft tissue infections may result from accidental inoculation of environmental NTM. Extrapulmonary or disseminated infections occur primarily in patients with immunodeficiencies [3], especially in advanced acquired immunodeficiency syndrome (AIDS).

Infrequently, NTM may cause musculoskeletal (MSK) infections, usually in immunocompetent hosts [1]. The most common NTM in MSK infection include MAC, M. marinum, and rapidly growing mycobacteria such as M. fortuitum, M. abscessus, and M. chelonae [4]. Tendon sheaths, bursae, joints, and bone can become infected after trauma, MSK surgery, invasive procedures, or deep skin puncture [4]. One study identified an iatrogenic outbreak of NTM septic arthritis following corticosteroid injections [5]. Superficial wounds acquired in the environment can also allow for invasion of various NTM species.

Of orthopedic cases, NTM infection is most often seen in the hand and wrist. In particular, digital flexor tenosynovitis is a common presentation [4, 6], as a result of the abundance of synovium in these areas and susceptibility to penetrating trauma. Due to the natural local degeneration of soft tissue associated with aging, MSK NTM infections are more likely to affect patients 50 years or older [6]. Increasingly, cases of vertebral osteomyelitis have been reported [7–9]. These are usually due to MAC but can less commonly be seen with M. abscessus [8]. M. marinum has also been on the rise, causing infectious tenosynovitis or septic arthritis after fish tank or other water exposure [10]. NTM may also cause PJI. In these cases, infection may occur immediately after implantation or as long as 25 years post-implantation [1]. The mean duration between onset of symptoms and diagnosis has been found to be 20.8 months [4].

Due to the indolent course of NTM, variabilities in clinical presentation, and often low index of suspicion, diagnosis can be difficult. NTM MSK infection should be considered if a patient has negative bacterial cultures and is resistant to traditional antibacterial therapy [7], especially in the setting of recent trauma to the area. Markers of systemic inflammation (ESR, CRP) may be elevated [1], though these can be normal as documented in case #1. AFB smear is often negative.

Tissue histopathology may reveal an array of inflammatory findings including caseating and noncaseating granulomas [4]. Imaging studies are helpful to evaluate disease extent. MRI has the highest sensitivity and specificity for detecting early osteomyelitis and providing detailed information on both bone marrow and periosteal inflammation [7, 11]. Expedient identification is particularly crucial in immunocompromised patients with a history of musculoskeletal surgery [1].

If AFB is identified, an interferon-gamma release assay (IGRA) may be helpful early on to differentiate NTM from M. tuberculosis while awaiting cultures [7]; however, several NTM species may result in a false positive IGRA. These include M. kansasi, M. marinum, and M. szulgai.

Surgical debridement is essential for treatment. In the case of osteomyelitis, there is often a heavy mycobacterial burden in bone marrow. Antimycobacterials alone cannot adequately penetrate necrotic bone. In the case of PJI, infected hardware should be explanted [4]. Pharmacotherapy is utilized following surgery to limit further spread and eliminate remaining mycobacteria. No guidelines currently exist for duration of therapy. One study in 14 cases found the median duration of antimycobacterial therapy was 14 months. Generally, therapy of six months up to two years is given depending upon the clinical response and the pathogen involved. Due to the variable nature of NTM species and high rates of drug resistance among some NTM, pharmacologic therapy should be determined after culture results yield drug susceptibilities [1, 6].

Due to the rarity of NTM bone and joint infections, outcomes and prognosis have not been defined. One small study showed relatively good prognoses in vertebral osteomyelitis due to NTM [12]. However, the long-term outcomes of musculoskeletal NTM infection depend upon host factors, extent of infection, success of surgical source control, and the organism itself.

The cases discussed here highlight the difficulties in both diagnosis and management of musculoskeletal NTM infections. A high index of suspicion is needed especially in cases with a predisposing mechanism of injury, such as penetrating trauma or previous orthopedic surgery. It is important to consider NTM in the setting of infections with a lack of response to standard antimicrobial therapy, negative routine bacterial cultures, and the presence of granulomata identified on tissue histopathology. Once a pathogen has been identified, surgical debridement and prosthetic removal is imperative, along with multi-drug therapy based on culture susceptibilities. Certain organisms, such as M. abscessus, may prove resistant to many drugs. Combination antimycobacterial therapy is required for a prolonged duration and is often difficult to tolerate.

Ethical approval

IRB approval from the University of Missouri.

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CRediT authorship contribution statement

Faith I. Vietor: Writing – original draft, Writing – review & editing, literature review. Taylor Nelson: Conceptualization, Writing – review & editing, Supervision.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. There is no identifiable patient information in the written manuscript, or the image provided.

Declarations of interest

None.

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