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Case Report

Extrapulmonary *Mycobacterium malmoense* infection in a patient with minimal immunosuppression

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ABSTRACT

Mycobacterium malmoense is an emerging non-tuberculous mycobacterial (NTM) pathogen that usually causes extrapulmonary disease, particularly, in significantly immunosuppressed patients. Recent reports from Scotland and the Netherlands, however, document an increasing proportion of pulmonary NTM infections due to *M. malmoense*, indicating a rising incidence in parts of Northern Europe—although still predominantly associated with pulmonary disease. We report a 78-year-old woman from north-eastern Germany with chronic tenosynovitis caused by *M. malmoense* under minimal long-term prednisone therapy. Diagnosis was established by histopathology, culture, and *hsp65* gene sequencing. Although up to 40% of reported *M. malmoense* infections are extrapulmonary, nearly all described tenosynovitis cases have occurred in children or in profoundly immunosuppressed adults. This case, therefore, represents an exceptionally rare clinical constellation, demonstrating that even minimal immunosuppression can permit infection with this slow-growing NTM. It further underscores the diagnostic complexity, along with the absence of clear guideline recommendations regarding optimal therapy duration, highlighting the need for individualized, multidisciplinary management.

Introduction

Nontuberculous mycobacteria (NTM) comprise more than 190 species, many of which are environmental organisms with variable pathogenic potential [1]. *Mycobacterium malmoense*, first described in Sweden in 1977, belongs to the *M. avium–intracellulare* complex–related group of slowly-growing NTM [2]. It has been mainly associated with pulmonary disease in Northern Europe and the United Kingdom, typically in patients with underlying structural lung disease or immunosuppression [2]. Extrapulmonary infections, including soft tissue and disseminated disease, are far less frequent and usually occur in severely immunocompromised individuals [2,3]. In contrast, cervical lymphadenitis is typically observed in immunocompetent children, with *M. malmoense* counted among the most common causative species alongside the *M. avium* complex and *M. haemophilum* [3].

The case

Patient

A 78-year-old female patient presented with a 16-month history of livid swelling and pain in her right distal forearm, hypothenar region, and fourth and fifth fingers. She had been on long-term prednisone therapy (2.5-5.0 mg/day) for over 10 years for disseminated joint pain, without confirmed evidence of an underlying autoimmune disease. There was no history of trauma. Physical examination revealed livid erythematous soft tissue swelling with warmth, most pronounced between the metacarpophalangeal and proximal interphalangeal joints of the palmar fifth finger, sparing the fingertip, and extending into the palmar aspect of the ulnocarpal compartment (Figure 1a).

Diagnostic workup and microbiological confirmation

Magnetic resonance imaging confirmed tenosynovitis without involvement of bony structures. Computed tomography of the chest and abdomen revealed no abnormalities. The interferon-γ release assay was negative. A deep dermal biopsy taken from

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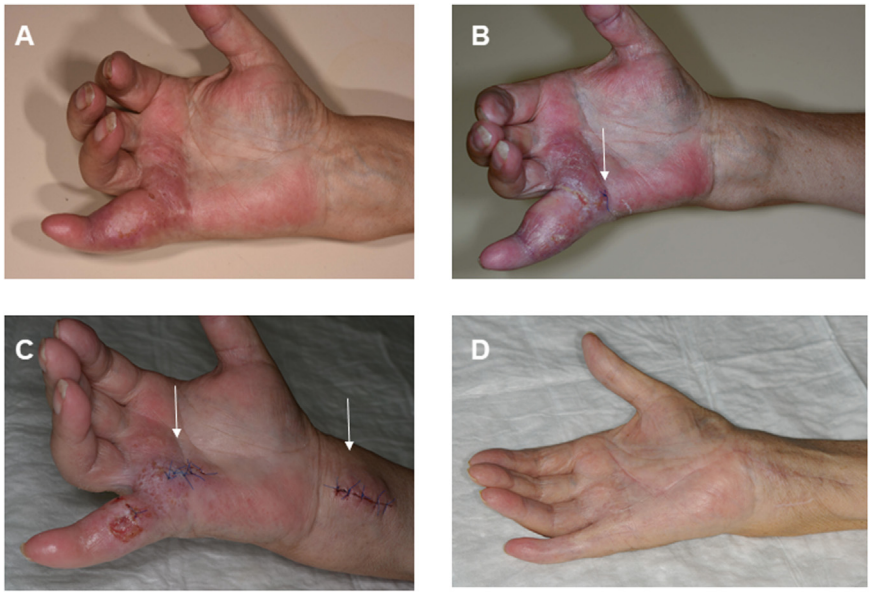

Figure 1. Clinical, diagnostic, and therapeutic course of a patient with chronic tenosynovitis due to *Mycobacterium malmoense*. (a) Clinical presentation of the right hand with livid erythematous soft-tissue swelling affecting the palmar aspect of the fifth finger and extending into the hypothenar region. (b) Biopsy site (arrow) from which histopathologic examination revealed fibrotic connective tissue with non-caseating granulomatous inflammation; subsequent microbiological culture yielded *M. malmoense*. (c) Post-synovectomy view (arrows); synovectomy performed as part of combined surgical and antimicrobial therapy. (d) Clinical resolution after 27 months of treatment with rifabutin, ethambutol, and clarithromycin, in conjunction with repeated surgical intervention.

the anatomical site indicated in Figure 1b (arrow) was submitted for histopathologic examination. Kinyoun staining demonstrated fibrotic and collagenous connective tissue with a non-caseating granulomatous inflammatory infiltrate composed predominantly of histiocytes, but no acid-fast bacilli were detected. Subsequent microbiological analysis of the tissue sample cultured *M. malmoense* after 12 days of incubation in a mycobacteria-specific culture system. The clinical isolate was cultured using the BACTEC MGIT 960 system (Becton Dickinson GmbH, Heidelberg, Germany). Species identification was performed by sequencing a 441 bp fragment of the *hsp65* gene, as previously described [4]. The sequence showed 99% identity to the *M. malmoense* reference strain CIP 105775 (GenBank accession no. AF547854.1), confirming the isolate as *M. malmoense*. Antimicrobial susceptibility testing was performed at the German National Reference Laboratory for Mycobacteria (Borstel, Germany), using a modified proportion method in liquid medium (BACTEC MGIT 960) and on solid media (Löwenstein–Jensen). The isolate was susceptible to rifabutin, ethambutol, clarithromycin, moxifloxacin, ciprofloxacin, amikacin, linezolid, and trimethoprim/sulfamethoxazole but resistant to rifampicin. Real-time polymerase chain reaction (PCR) targeting the *M. tuberculosis complex* and pan-mycobacterial PCR confirmed the presence of *M. malmoense*.

Therapeutic approach and clinical outcome

Oral antituberculous therapy was initiated with rifabutin (300 mg/day), ethambutol (600 mg/day), and clarithromycin (500 mg twice daily). This regimen aligns with current consensus recommendations for treating NTM infections, including *M. malmoense* [5], and was well tolerated. Prednisone therapy was discontinued, and the patient underwent two synovectomies (Figure 1c, arrows). She received anti-infective therapy for 27 months, achieving complete symptom resolution (Figure 1d).

Clinical and epidemiological relevance

M. malmoense, a member of the NTM group, has garnered attention due to its clinical relevance and increasing incidence in various populations. A recent systematic review and meta-analysis has detailed the clinical spectrum, epidemiologic characteristics, and treatment outcomes of *M. malmoense* infections [2]. In Denmark, a marked rise in pulmonary NTM infections was observed between 1991 and 2022, with *M. malmoense* identified as one of the leading species alongside *M. kansasii* and *M. avium* complex [6]. Similarly, Brode et al. analyzed over 26,000 NTM isolates in Ontario (1998-2010) and found that non-pulmonary sites accounted for only about 4% of NTM cases, with pulmonary isolates predominating. They concluded that pulmonary NTM disease primarily affects individuals with preexisting lung conditions or structural abnormalities, whereas non-pulmonary NTM infections—such as in our patient—are more common in the context of immunosuppression or NTM entry into breached tissue [7]. In contrast, Piersimoni et al. [8] reported that localized non-pulmonary NTM infections often occur in immunocompetent individuals, suggesting a more nuanced interplay between host immunity and site of infection. In their analysis of musculoskeletal infections they noted that "most affected patients are immunocompetent," although they acknowledged that certain species (e.g. *M. chelonae, M. hemophilum*) more commonly affect immunocompromised hosts. These findings point to species-specific pathogenic behaviors rather than a uniform dependency on immune status. Geographic variability in NTM species distribution and associated clinical presentations further complicates the epidemiologic landscape. For instance, Prevots and Marras [9] reported that *M. avium* is the most frequently isolated species causing pulmonary disease in most regions of the world. Of note, however, are the high percentages of pulmonary NTM infections caused by *M. xenopi* in Croatia, Czech Republic, and Serbia; by *M. kansasii* in Poland and certain Spanish regions; and by *M. malmoense* in Scotland and the Netherlands, highlighting the regional clinical relevance of our patient's infection. All in all, the rising frequency of NTM isolation in various settings indicates that *M. malmoense* may be emerging as a significant pathogen in certain populations, necessitating further investigation into its epidemiology and clinical impact. This complexity is further illustrated by pediatric NTM infections in which *M. avium* is the predominant species causing lymphadenitis [10].

Comparative cases

The clinical presentation of *M. malmoense* infections often varies with the host's underlying health status—a distinction relevant for diagnostic and therapeutic decisions. Interestingly, our patient, such as five cases involving *M. marinum, M. kansasii, M. szulgai*, or *M. nonchromogenicum* infections [11], has been of Middle-European descent. Although *M. malmoense* is more frequently associated with pulmonary disease in immunocompromised patients [6,7], this case shows that it can also cause clinically significant non-pulmonary infection in individuals with minimal immunosuppression. We present evidence that even low-dose prednisone in an otherwise systemically well patient was sufficient to favor chronic *M. malmoense* tenosynovitis. This indicates that non-pulmonary *M. malmoense* disease (although rare) may emerge regardless of host immune status—a finding consistent with those of Wetzstein et al. [2] who report that such cases predominantly occur in otherwise healthy children and only very rarely in patients with HIV or other severely immunocompromised patients. Elsewhere, Kim et al. [12] described flexor tenosynovitis due to *M. haemophilum*, highlighting synovitis as a recognized manifestation of NTM infections in the hand. This underscores the importance of considering NTM in chronic tenosynovitis where diagnosis is often delayed [11,12].

Treatment recommendations

Although established treatment protocols exist for pulmonary NTM infections, the optimal therapy—particularly, its duration—for NTM tenosynovitis remains uncertain [12]. Prolonged, combined surgical and antibiotic treatment may be necessary, especially in immunocompromised patients and in refractory cases [12]. For pulmonary disease, standard treatment typically includes rifampicin, ethambutol, and clarithromycin, with alternatives such as moxifloxacin or clofazimine in cases of resistance or intolerance [5]. Despite evidence from two randomized controlled trials guided by the British Thoracic Society (BTS NTM trials) and three cohort studies (two from the UK, including Cardiff and Edinburgh, and one from the Netherlands), recommendations for *M. malmoense* treatment remain based on low-quality evidence [5]. For NTM tenosynovitis, Kim et al. [12] emphasize that treatment often involves surgical debridement and antimicrobial therapy, typically lasting 6-12 months; in their report, patients received a regimen of rifampicin, ethambutol, and clarithromycin, with some requiring additional drugs such as amikacin or azithromycin, depending on resistance. The mean duration of treatment was 9.8 months, highlighting the importance of personalized approaches and multidisciplinary management, particularly, in the absence of clear consensus for non-pulmonary *M. malmoense* disease [12].

Diagnostic challenges and methodological considerations

Species-level identification by *hsp65* sequencing is critical for distinguishing *M. malmoense* from *M. tuberculosis* and other NTM species due to their overlapping clinical presentations and radiological findings [13]. Indeed, granulomatous inflammation identified histopathologically, although suggestive, cannot reliably differentiate among mycobacterial species. Similarly, broad-range molecular assays (e.g. pan-mycobacterial PCR targeting mycobacterial 16S ribosomal ribonucleic acid) affirm the genus-level presence of *Mycobacterium* but are insufficient to definitively specify NTM species, particularly, when discriminating from closely related organisms such as *M. haemophilum* [14]. In line with previous reports, this case highlights that precise, species-specific molecular methods—such as *hsp65* gene sequencing—are essential for accurate diagnosis and effective clinical management [14]. Taken together, although histologic and generic PCR methods provided valuable ancillary support, definitive diagnosis of *M. malmoense* required specific molecular identification through culture-derived *hsp65* sequencing, emphasizing the necessity for targeted molecular diagnostics to guide appropriate treatment decisions.

Position of the case in the literature

Prevots and Marras [9] reported that *M. malmoense* is increasingly encountered in Northern Europe, although almost exclusively in the context of pulmonary disease. In parallel, Wetzstein et al. found that although approximately 40% of *M. malmoense* cases are extrapulmonary, nearly all tenosynovitis cases occurred in children or profoundly immunocompromised patients [2]. Our case of chronic tenosynovitis in an elderly woman with minimal immunosuppression, therefore, represents a clinical constellation essentially absent from the published literature. Moreover, it conveys an important clinical message that the degree of immunosuppression conferred by long-term, low-dose glucocorticoid therapy is often underestimated and variably defined in practice and that even such modest doses may predispose to opportunistic infections, such as *M. malmoense*.

Conclusion

M. malmoense represents a significant and emerging NTM pathogen with increasing incidence and diverse clinical presentations. Clinicians need to be aware of non-pulmonary and extranodal presentations, particularly, tenosynovitis. The risk increases with any form of immunosuppression. Accurate species-level diagnosis via culture and *hsp65* sequencing is essential to distinguish *M. malmoense* from tuberculosis and other NTM infections. Improved surveillance and tailored treatment protocols, informed by ongoing research into the epidemiology, pathogenesis, and clinical characteristics of *M. malmoense* infections, remain essential for improving public health strategies and clinical practice.

Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Antonios Katsounas: Writing – original draft, Conceptualization, Writing – review & editing. **Gernot Geginat:** Writing – review & editing, Resources. **Jon S Friedland:** Writing – review & editing, Supervision.

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Ethics and approval statements

This work is a retrospective case report based on fully anonymized clinical data from a lost-to-follow-up patient. The ethics committee of the Otto-von-Guericke University Hospital Magdeburg reviewed the case and waived the requirement for formal ethics approval under applicable German and European Union regulations because it did not fall under the scope of formal human subjects research review.

Authorship

All authors meet the 4 ICMJE criteria for authorship. ORCID identifiers are provided for all authors, including the first (corresponding) author. Written permission was obtained from all persons listed as authors.

Other disclosures

All authors confirm and acknowledge the following: This manuscript (or one with substantially similar content written) has not been published previously. Images or tables have not been previously published elsewhere.

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