Case Report

First report of tenosynovitis in an immunocompetent person caused by *Mycobacterium heraklionense*

Malak Abedalthagafi,¹,² Oren Rosenberg³ and Steve Miller¹

¹Department of Laboratory Medicine, University of California San Francisco, San Francisco, CA, USA
²Department of Pathology, Brigham and Women’s Hospital, Harvard University, Boston, MA, USA
³Department of Medicine, Division of Infectious Diseases, University of California San Francisco, San Francisco, CA, USA

Introduction: *Mycobacterium heraklionense* is a newly described species member of the *Mycobacterium terrae* complex.

Case presentation: We have described a case of chronic tenosynovitis caused by *M. heraklionense* using 16S rRNA gene sequencing. The infection was associated with trauma and foreign-body introduction in an otherwise healthy patient.

Conclusion: *M. heraklionense* appears to have worldwide distribution and has the ability to cause disease similar to other members of the *M. terrae* complex.

Keywords: ethambutol; granuloma; mycobacteria; tenosynovitis.

Introduction

*Mycobacterium heraklionense* is a newly proposed species closely related to *Mycobacterium arupense* and is a member of the *Mycobacterium terrae* complex (MTC) (Tortoli et al., 2013). *M. heraklionense* has an intermediate growth rate and is unpigmented. It is proposed to be named after Heraklion, the city in Crete where many strains were isolated. The utility of biochemical tests and mycolic acid analyses for the differentiation of the members of the MTC is limited. However, *M. heraklionense* is distinguishable from other MTC members by unique sequences in 16S rRNA, hsp65 and rpoB genes (Tortoli et al., 2013). Since the initial description of three previously undescribed species of MTC in 2012 (*Mycobacterium engbaekii*, *M. heraklionense* and *Mycobacterium longobardum*), there has been one report of infection caused by *M. longobardum* (Hong et al., 2013). Here, we describe the first report, to our knowledge, of infection caused by *M. heraklionense*: a chronic tenosynovitis associated with trauma and foreign-body introduction in an otherwise healthy individual.

Case report

A 37-year-old male with no significant medical history was pruning fruit trees in his usual capacity as an agricultural worker and was injured when a thorn from a lemon tree lodged into his left middle finger. The hand swelled slightly, but he had no fever or chills. Two months later, he went to his doctor with mild pain, tenderness and trouble moving the third digit on his left hand. His primary physician noted swelling and tenderness at the level of the proximal phalanx, limited proximal interphalangeal joint flexion and extension with normal circulation, no drainage and no erythema. The patient’s symptoms were thought to be a reaction to the foreign body and the patient was referred to surgery to remove any debris from the hand. The surgery revealed intense inflammation with flexor tenosynovitis but no evidence of a foreign body. The pathology showed acute synovitis with abundant macrophages and rare giant cells; a Grocott’s methenamine silver (GMS) stain for fungal organisms was negative. A bacterial culture of a swab specimen was performed at this time but showed no growth. He continued to have signs of infection with increased swelling and redness, wound dehiscence and expressed pus. A second exploratory procedure 2 months later demonstrated proliferative tenosynovitis in the left palm and third digit, but again no foreign body was encountered. Tissue from his left middle finger was submitted for bacterial, fungal and acid-fast bacillus (AFB) cultures. The pathology showed chronic inflammation with giant cell reaction, granuloma formation and focal abscess (Fig. 1a). GMS and acid-fast stains were negative for organisms.

Investigations

The fungal culture was noted to have pinpoint colonies after 19 days of incubation; these were non-pigmented,
stained Gram-positive to Gram-variable and were acid-fast by Kinyoun stain (Fig. 1b–d). The AFB colonies were inoculated into a broth vial and submitted for molecular characterization to the University of Washington Molecular Diagnosis Microbiology Section (Seattle, WA, USA) for AFB sequencing of cultured organisms. For species identification, 16S rRNA gene sequencing using universal primers was carried out. A BLAST search of the sequence obtained was performed using the taxonomy browser of the National Center of Biotechnology Information (http://blast.ncbi.nlm.nih.gov/Blast.cgi). As a result of 16S rRNA gene sequencing, the organism was identified as *M. heraklionense*. Based on this information, a course of therapy was initiated with rifabutin, ethambutol and azithromycin. The identification was confirmed using 16S rRNA gene sequencing at the National Jewish Center for Respiratory Diseases (Denver, CO, USA).

Susceptibility testing was performed at the National Jewish Center for Respiratory Diseases using Clinical and Laboratory Standards Institute guidelines for slowly growing non-tuberculosis mycobacteria with interpretation derived from *Mycobacterium kansasii* breakpoints (CLSI, 2011). The results showed the following MIC values (μg ml⁻¹): amikacin, 8 (S); ciprofloxacin, >4 (R); clarithromycin, ≤4 (S); clofazimine, 0.5; ethambutol, 2.5 (S); rifabutin, ≤0.12 (S); rifampin, ≤0.5; and streptomycin, 8. Using a combination of rifampin and ethambutol, the effect was additive and yielded a rifampin MIC of 0.25 μg ml⁻¹ and an ethambutol MIC of 1.25 μg ml⁻¹.

**Treatment**

The patient was started on a regimen of rifabutin 300 mg daily, ethambutol 1200 mg daily and clarithromycin 500 mg twice daily for 2 weeks, but he developed severe nausea and the clarithromycin was switched to azithromycin 500 mg daily, after which he tolerated the medications well. After about 3 months on this regimen, he developed severe neutropenia and all medications were stopped. He was untreated for 2 months during which time he had a complete recovery of the blood counts, but on follow-up, his hand was found to be more swollen, although not red, tender or warm. He was restarted on azithromycin 500 mg daily and ethambutol 1200 mg daily, on which he continues at this time.

**Discussion**

*M. terrae* was first isolated in 1950 from radish washings and is described as an acid-fast saprophyte (Richmond & Cummings, 1950). MTC are Runyon group III and non-pigmented, with an intermediate growth rate (5–15 days are required for the development of clearly visible colonies from dilutions inoculated on solid medium). DNA probes specific for species of the MTC have not been introduced in any of the commercial kits. MTC organisms are uncommon pathogens causing a variety of skin and soft-tissue infections (Wayne, 1985; Wayne et al., 1986). Classically, biochemical characterization and high-performance liquid chromatography analysis of mycolic acids have been used for species identification, but this approach does not have sufficient power to distinguish between closely related species, which are separated using DNA sequence analysis (Ridderhof et al., 1991).

The differential diagnosis of chronic infectious causes of tenosynovitis includes a variety of organisms including non-mycobacterial organisms. A review of 54 patients (Smith et al., 2000) indicated that infection with MTC could result in debilitating disease, most commonly tenosynovitis of the hand: 32 of the 54 patients had either a history of trauma after an antecedent puncture of the hand, or an occupation or hobby that increased the risk for hand trauma such as farming, gardening, butchering and cooking. Most of the patients in the review had no predisposing conditions similar to our case, although it is difficult to rule out specific genetic variation that could lead to increased susceptibility (for example, mutations in the IL-12–IL-23–IFN-γ axis; Chapman & Hill, 2012). Most of the patients were treated with multiple antibiotics. Despite the absence of underlying conditions, 31% of the patients had persistent or recurrent infection, and two of the three reported amputations were performed in patients with no other medical conditions.

An Italian study published recently (Tortoli et al., 2013) first described *M. heraklionense* as a separate species by 16S rRNA, *rpoB* and *hsp65* gene sequencing. Banked isolates were included from patients with a variety of clinical
conditions including renal/heart failure, MDS (myelodysplastic syndrome), lung cancer, tuberculosis, lymphoma, rheumatoid arthritis, pulmonary fibrosis and chronic obstructive pulmonary disease. Most specimen types were not described but those that were included bronchoalveolar lavage and sputum. A majority of the patients with known ages were >60 years. Whether these isolates were considered clinically significant is not known. The isolates from this study were described as sensitive to clarithromycin and rifabutin and resistant to quinolones, rifampicin, sulfamethoxazole and doxycycline. Of particular interest is the treatment of such infections, as very little guidance is available. The American Thoracic Society guidelines state that the optimal treatment of nontuberculosis mycobacterial infections has not been established but anecdotally recommends a macrolide with ethambutol for a duration of 4–6 months of therapy, depending on concern for bone involvement (Kasperbauer & Huit, 2013).

To our knowledge, this is the first described case of definitive infection caused by *M. heraklionense*, which appears to have a worldwide distribution and pathogenic potential. The infection was associated with trauma and foreign-body introduction in an otherwise healthy patient. Further studies will be needed to determine the frequency and pathogenicity of *M. heraklionense* and whether this differs from other members of the MTC.

**Acknowledgements**

The authors declare no conflict of interest.

**References**


