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## Case Report

Flexor Tenosynovitis Caused by *Mycobacterium heraklionense*

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*Mycobacterium heraklionense* is a rare etiology of serious hand infection with only 2 cases having been reported in literature to date to our knowledge. We describe the case of a 58-year-old woman with persistent swelling and stiffness in her right index finger. Advanced imaging studies in addition to serial surgical debridement with tissue cultures helped to confirm the diagnosis of flexor tenosynovitis caused by *M. heraklionense*. In this case report, we highlight the clinical evaluation, operative treatment, and antimicrobial therapy leading to the successful care of this disease presentation. Due to its rarity and potential to cause substantial hand infection, *M. heraklionense* should be included in the differential diagnosis as the cause for chronic flexor tenosynovitis to appropriately minimize morbidity.

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The presentation, treatment, and outcome of flexor tenosynovitis (FTS) caused by atypical organisms such as mycobacteria are infrequently described in the literature. These atypical infections usually demonstrate an indolent course with chronic disease resistant to standard anti-infective therapies. *Mycobacterium marinum* is the most common mycobacterium species associated with soft tissue hand infections, particularly following marine exposure.<sup>1</sup> *Mycobacterium avium intracellulare* is the most common isolate in deep infections of the hand and causes granulomatous tenosynovitis, especially in patients with weakened immunity.<sup>1</sup> *Mycobacterium heraklionense*, a newly proposed species of the *Mycobacterium terrae* complex (MTC), is an unpigmented atypical mycobacterium with an intermediate growth rate.<sup>2</sup> To date and to our best knowledge, there have been only 2 published case reports of *M. heraklionense* implicated FTS.<sup>3,4</sup> In this article, we describe an additional case of FTS caused by *M. heraklionense* and review the current literature to highlight the various obstacles in establishing the correct diagnosis and the specific treatment considerations for this uncommon disease presentation.

**Declaration of interests:** No benefits in any form have been received or will be received related directly or indirectly to the subject of this article.

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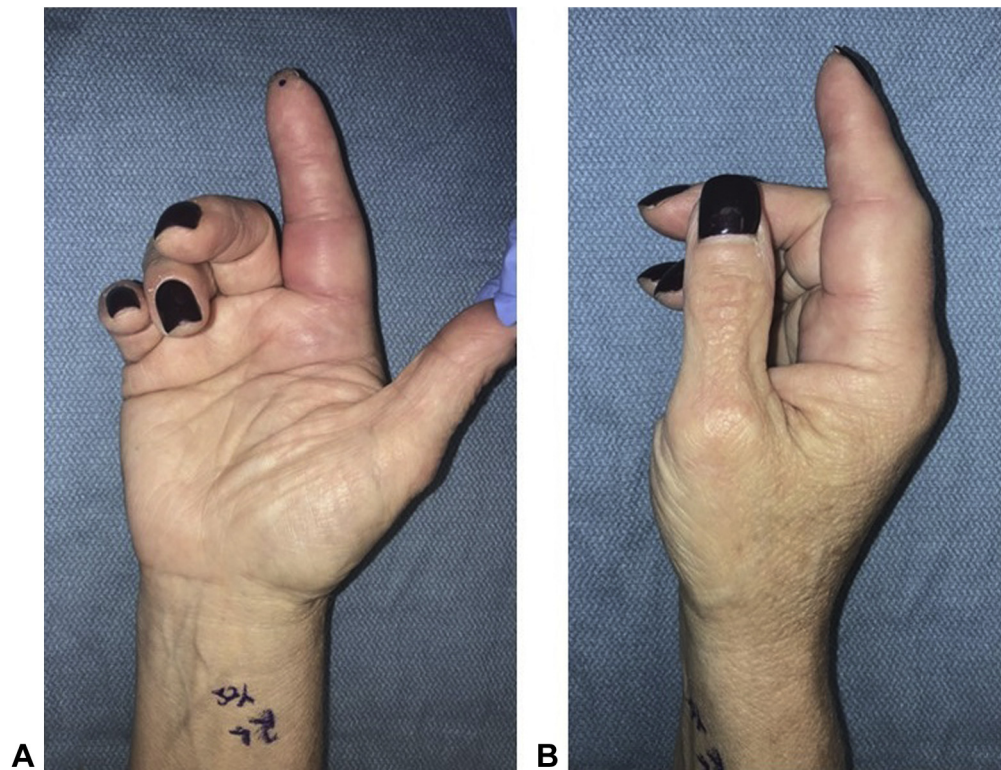
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## Case Report

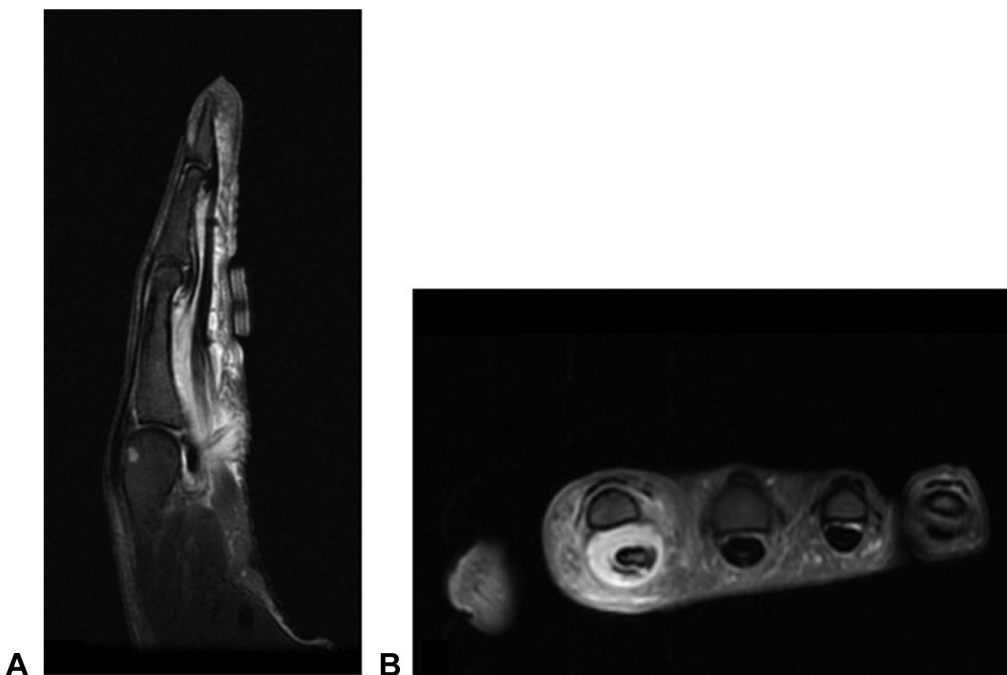
A 58-year-old woman first presented to another hand surgeon with 4 weeks of right index finger pain, swelling, and stiffness (Fig. 1). Her past medical history was notable for hypertension, epilepsy, and lupus. She previously took immune-modulating agents for her autoimmune disease but had recently ceased for an upcoming spinal surgery. She denied any systemic symptoms or hand trauma. However, she did report that during her seizures she sometimes sustained unknown injuries. She was initially diagnosed with dactylitis, treated with a corticosteroid injection into the first annular pulley (A1 pulley) to reduce the swelling and pain, and prescribed therapy for range of motion exercises. Her condition did not improve with these interventions, and she sought further evaluation in our clinic.

The patient presented to our clinic 4 weeks after visiting the outside physician. We obtained advanced imaging with magnetic resonance imaging and ultrasound to better evaluate her finger swelling. Both studies demonstrated fluid within the flexor tendon sheath without evidence of osteomyelitis (Fig. 2). In addition, on physical examination she had tenderness over her volar middle and proximal phalanges of the involved digit and proximal to the A1 pulley. Her laboratory markers were unremarkable and all within the normal laboratory limits, and she was HIV seronegative.

The concern for FTS due to her physical examination and imaging findings was discussed with the patient, and she agreed to proceed with surgical debridement. The initial plan was to proceed with a limited debridement to obtain cultures and tissue for



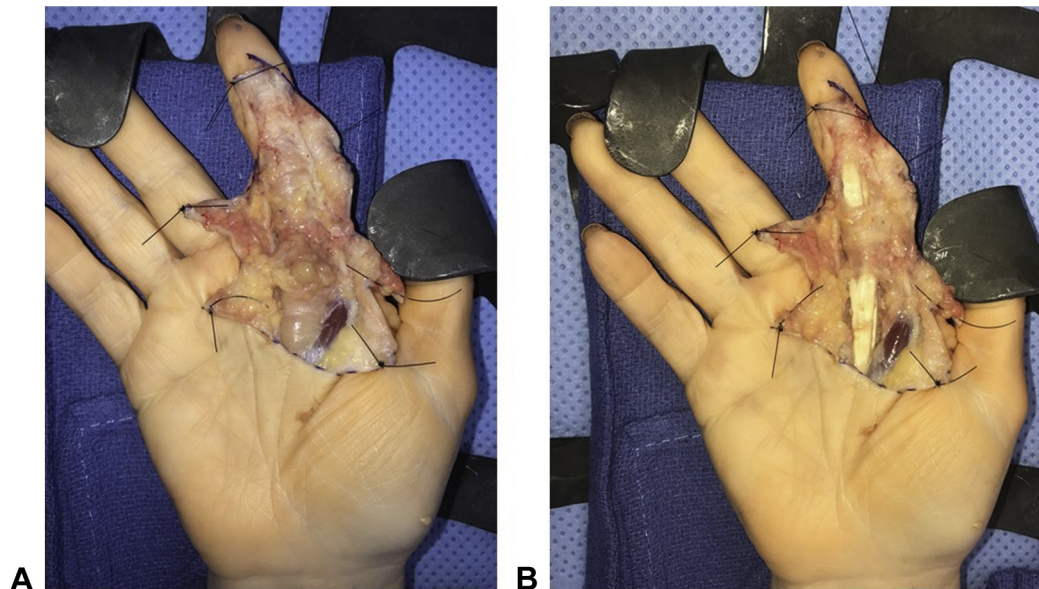
**Figure 1.** Preoperative clinical photograph showing the initial presentation, with fusiform swelling, stiffness, and erythema of right index finger. **A** Frontal view and **B** side view of involved digit.



**Figure 2.** Preoperative advanced magnetic resonance imaging of the **A** sagittal T2-weighted fat suppression and **B** axial proton density fat suppression sequences of the patient's hand showing fluid within the flexor sheath of the index finger. Over 3 mm of separation of the flexor tendons from the phalanx at the proximal phalanx indicates pulley injury or attenuation.

pathology and then return for definitive treatment after the diagnosis was established, if necessary. In the operating room, upon first entering the right index finger flexor tendon sheath with a transverse incision at the level of the A1 pulley, tan, fleshy, and

solid-appearing tissue and murky fluid was encountered. This extensive synovitis within the flexor tendon sheath was debrided and sent for pathology. Cultures of the synovial fluid were taken for bacterial, fungal, and acid-fast bacteria (AFB). No frank purulence



**Figure 3.** Intraoperative clinical photograph showing **A** before and **B** after debridement with removal of inflammatory tissue from flexor tendon sheath.

was encountered. A second incision was made for the initial limited exposure on the midlateral aspect of the digit just distal to the fifth annular pulley to further irrigate the flexor tendon sheath.

Results from the initial debridement showed tissue histology with acute and chronic inflammation and negative bacterial cultures. A whole-blood *Mycobacterium tuberculosis* test (Quantiferon-TB Gold, Qiagen) was obtained due to the elevated level of suspicion for atypical infection and desire to obtain a preliminary diagnosis sooner than with AFB cultures. Based on clinical suspicion and a positive whole-blood test, she was diagnosed with a mycobacterial infection and started on a combination regimen including isoniazid, rifampin, ethambutol, pyrazinamide, azithromycin, and moxifloxacin. She had considerable difficulty with tolerance of this regimen, limiting her adherence. Subsequently she reported increasing pain, swelling, and erythema of the right hand, as well as subjective fevers at 5.5 weeks after the index procedure. At this time, a repeat ultrasound indicated persistent tenosynovitis with new complex tissue contents within the flexor tendon sheath. Tissue cultures (4 weeks after the initial surgery) yielded AFB growth in 1 of 2 surgical specimens.

Based on the progressing clinical picture, the consensus was to proceed with repeat surgical debridement 6 weeks after the index surgery. During this procedure, Bruner incisions were used for open debridement of the finger (Fig. 3). A window was made between the second and fourth annular pulleys to expose and debride the tendon sheath and flexor tendons themselves, which were markedly adhered to the infective tissue and to each other. Repeat histology was consistent with classical findings of acute and chronic granulomatous inflammation (Fig. 4).

The AFB growing via tissue culture underwent molecular sequencing by request of the physician team, confirming the species as *M. heraklionense*. This allowed for narrowing of antibacterial therapy, and full sensitivities returned 1 week after speciation. This strain of *M. heraklionense* showed susceptibility to clarithromycin, rifabutin, rifampin, ethambutol, amikacin, and linezolid, with resistance to ciprofloxacin, moxifloxacin, and trimethoprim-sulfamethoxazole.

Postsurgical management focused on continuation of antimicrobial therapy with rehabilitation to optimize functionality of the digit. The patient was treated with an additional 12 months of

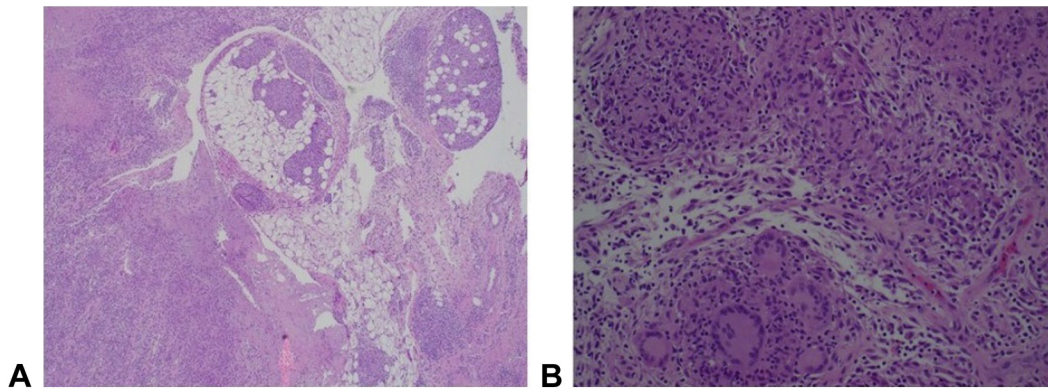
combination therapy from her second debridement consisting of daily azithromycin (500 mg), ethambutol (1200 mg), and rifabutin (300 mg). She experienced nausea and gastrointestinal upset attributed to the azithromycin, which was alleviated with antiemetics.

After 1 year of antimicrobial therapy, repeat magnetic resonance imaging of the right hand showed resolution of her FTS, and she was able to discontinue her antimicrobial regimen. Currently the patient is over 2 years from initial presentation, has no pain, and has returned to her previous level of activity and work inside the home. She continues her self-directed hand therapy for residual stiffness (Fig. 5). The patient provided written informed consent for publication of this case report.

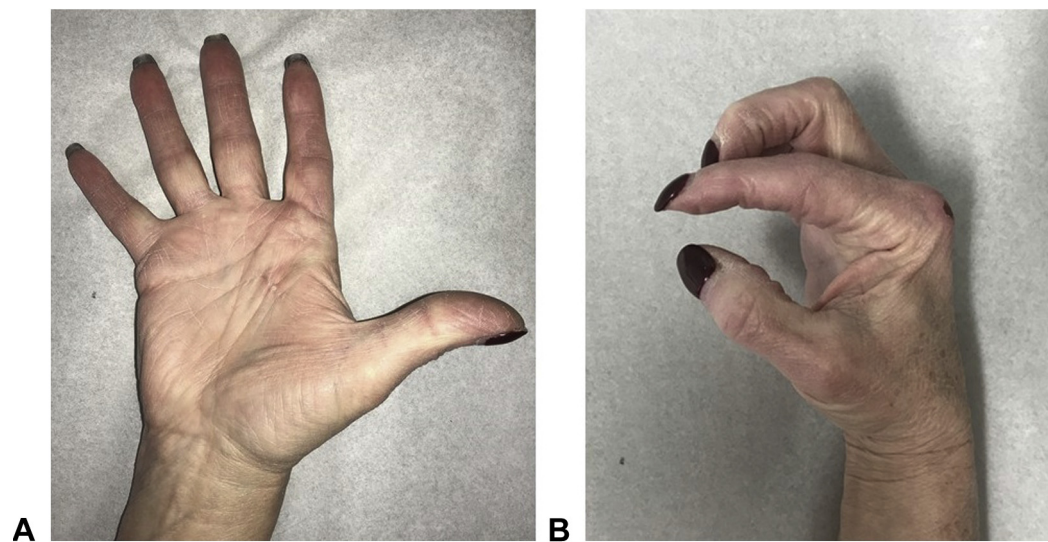
## Discussion

Flexor tenosynovitis is a closed-space infection of the hand flexor tendon sheath and can lead to serious morbidity, especially stiffness, if inadequately treated. Most often this condition is caused by skin flora; however, rarely it can be caused by atypical mycobacteria. In the 2 previously published case reports of *M. heraklionense* FTS, both patients went on to develop chronic disease with substantial finger swelling and stiffness due to delayed diagnosis. Eradication of the infection was finally realized after serial debridement and multiagent antimicrobial therapy tailored for the susceptibility of *M. heraklionense* strain.<sup>3,4</sup>

*Mycobacterium heraklionense* was first described in 2013. It is a subspecies within the MTC and exhibits an intermediate growth rate, classically developing colonies within 5 to 12 days at incubation temperatures of 25–37 °C.<sup>5</sup> Historically, MTC was considered an environmental sputum contaminant, but series of cases described the occurrence of osteomyelitis and tenosynovitis; often associated with puncture injuries. The MTC initially consisted of 2 slow growing species, *Mycobacterium nonchromogenicum* and *M. terrae*, as molecular methods were unavailable to differentiate into more distinct species potentially resulting in mischaracterization of pathogenic potential.<sup>6</sup> Accordingly, a study by Vasireddy et al<sup>6</sup> using genetic sequencing to characterize previous cases of tenosynovitis attributed to *M. terrae* found they were often identified as other species within the MTC family, with 38% identified as



**Figure 4.** Pathology imaging of debrided inflammatory tissue, demonstrating granulomatous inflammation with giant cells, Hematoxylin-eosin stain; magnification 100–400x, **A** low power and **B** high power.



**Figure 5.** Postoperative clinical photograph of the patient, demonstrating reduced swelling and the patient's **A** full extension but **B** still limited maximal index finger flexion at 15 months after the initial presentation.

*Mycobacterium aurupense* and 38% as *M. heraklionense*. In their review, all the isolates were susceptible to clarithromycin and rifabutin, with high in vitro sensitivity to ethambutol (92%) and trimethoprim-sulfamethoxazole (70%), and rates of resistance to rifampin, quinolones, and tetracyclines were high.<sup>6</sup> The duration of therapy is undefined as the aggressiveness of surgical debridement, patient comorbidities, immune status, and the longitudinal clinical response likely all factor into this decision. A review of 11 cases of tenosynovitis caused by the closely related species *M. arupense* cited treatment ranges from 4 to 14 months of therapy.<sup>7</sup>

While the antibiotic choice and duration continue to be refined, the most critical aspect in management of these cases is establishing the diagnosis. Most reported cases have a delayed diagnosis such that a high clinical index of suspicion is required, particularly in cases of progressive chronic synovitis when routine bacterial cultures are negative. Presumptive suspicion for mycobacterium should be raised when tissue biopsy and histologic specimens indicate granulomatous changes. Our case, similar to prior literature, required more than 1 debridement procedure. Additionally, growth of *M. heraklionense* occurred in only 1 tissue sample. Therefore, obtaining several tissue specimens, and potentially pursuing serial debridement procedures to establish a diagnosis, is important. Additionally, incubation at several temperatures can optimize potential culture yield. Coordination with the laboratory

with mycobacterial culture incubation at 30 °C, 37 °C, and 42 °C is recommended. Classically, *M. marinum*, *Mycobacterium haemophilum*, and *Mycobacterium ulcerans* have been found to grow best at 30 °C, while *Mycobacterium xenopi* grows at 42 °C, and the rest of the mycobacterial varieties exhibit optimal growth at 37 °C.<sup>6</sup>

In patients with a high suspicion for mycobacterial disease, fresh tissue specimens sent for broad array molecular DNA sequencing may be invaluable to establishing a diagnosis due to the fastidious nature of these organisms. However, culture results are still the gold standard, as molecular diagnostics do not provide antibiotic sensitivity testing and can produce results that conflict with cultures or are unlikely to be pathogenic. Ultimately, the cornerstone of management is debulking of disease burden and aggressive surgical debridement, sometimes serially, with combination antimicrobial therapy generally including 3 agents and driven by sensitivities. Establishing a culture diagnosis is especially pertinent, as each mycobacteria species has distinct resistance profiles. Close collaboration between subspecialties is also important to balance medication adverse effects and adjust therapy based on clinical course.

In this case report we describe the presentation, diagnosis, and treatment of FTS caused by *M. heraklionense*. To our knowledge, this is only the third definitively identified presentation of FTS caused by this pathogen. In this article we provide a detailed outline of the steps and reasoning behind our diagnostic workup and treatment

protocol. Based on our patient's case, we recommend early advanced imaging when the diagnosis of chronic FTS is in question, serial debridement to establish local control, and a multidisciplinary approach to treatment with emphasis on the partnership with infectious diseases colleagues when encountering atypical mycobacterial infections in the hand.

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