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Case report

Osteomyelitis due to *Mycobacterium haemophilum* in an adult renal transplant recipient

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ABSTRACT

Mycobacterium haemophilum is an increasingly recognized pathogen of the non-tuberculous mycobacteria family that largely infects immunocompromised adults and immunocompetent children. *M. haemophilum* is a fastidious and slow-growing organism that exhibits preferential growth at lower temperature with iron supplemented media, and therefore most clinical manifestations involve cutaneous infection or musculoskeletal infection of the distal extremities. It is believed that opportunistic infection occurs in immunocompromised hosts when the organism is acquired through environmental exposure. We describe the case of a 71-year-old renal transplant recipient who developed acute *M. haemophilum* osteomyelitis of the left foot, likely contracted from Epsom salt soaks with contaminated tap water. Outcomes of *M. haemophilum* infection are generally favorable in the literature. Our patient was treated with local debridement and partial amputation followed by a 3-drug antimycobacterial regimen until definitive amputation could be completed.

Case presentation

A 71-year-old man with a two-year history of deceased donor kidney transplantation presented to the Emergency Department with a one-week history of progressive left foot pain and swelling. On presentation his immunosuppressive regimen included daily prednisone, twice daily mycophenolate mofetil, and monthly belatacept infusions. The remainder of his medical history included coronary artery disease and type 2 diabetes mellitus, complicated by neuropathy, nephropathy, and end stage renal disease, for which he had undergone renal transplantation. The patient reported nightly Epsom salt (magnesium sulfate) soaks of his feet for the last several years. One week prior to presentation he struck his left hallux against the dining table leg with traumatic avulsion of the toenail. This injury was followed by progressive pain and swelling of the foot and purulent drainage from the nailbed wound.

Upon hospital presentation his temperature was 36.2 °C (97.2°F) and physical examination revealed marked swelling, erythema, and warmth of the left foot with purulence noted from the hallux nailbed wound. Laboratory evaluation revealed a white blood cell count of 4000/mm^3 (normal 3700–10,000/mm^3), a serum creatinine of 1.18 mg/dL (within the patient's post-transplant baseline), an erythrocyte sedimentation rate of 83 mm/hr (normal 0–20 mm/h), and a C-reactive protein of 0.99 mg/dL (normal <0.5 mg/dL). Magnetic Resonance Imaging (MRI) of the left foot demonstrated acute multi-focal osteomyelitis involving the distal first and fourth phalanges, as well as the middle second and third phalanges (Fig. 1). A superficial wound culture obtained from the nailbed demonstrated growth of methicillin-susceptible *Staphylococcus aureus* and pan-susceptible *Klebsiella pneumoniae* on routine aerobic culture. The Infectious Disease service was consulted and recommended a 6-week course of cefazolin for treatment of acute osteomyelitis, as the patient initially declined amputation.

Inflammatory markers continued to rise on serial laboratory monitoring (CRP 3.07 mg/dL after 13 days of therapy and CRP 7.69 mg/dL after 20 days of therapy), prompting short term follow-up imaging to assess for additional complications such as abscess formation. Repeat left foot MRI after 3 weeks of antimicrobial therapy revealed progressive osteomyelitis now involving the proximal portions of the first and fourth phalanges. The patient subsequently underwent operative debridement of the affected digits with partial amputation of the first phalanx. Pathology of bone specimens revealed residual acute osteomyelitis at the resection margins and abundant acid-fast bacilli on auramine-rhodamine fluorochrome stains of all specimens (Fig. 2). The patient underwent completion left trans-metatarsal amputation which demonstrated heavy bacterial burden within the resected bone (Fig. 3).

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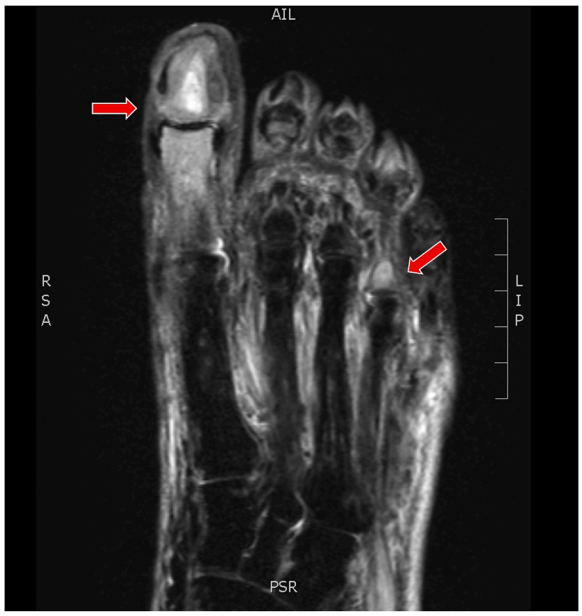

Fig. 1. Abnormal T1-weighted STIR bone marrow signal involving the first digit extending into the middle phalanx, with additional abnormal bone marrow edema within the middle second and third phalanges, and abnormal bone marrow signal in the middle fourth phalange, as indicated by red arrows. (Left foot Magnetic Resonance Imaging, axial view).

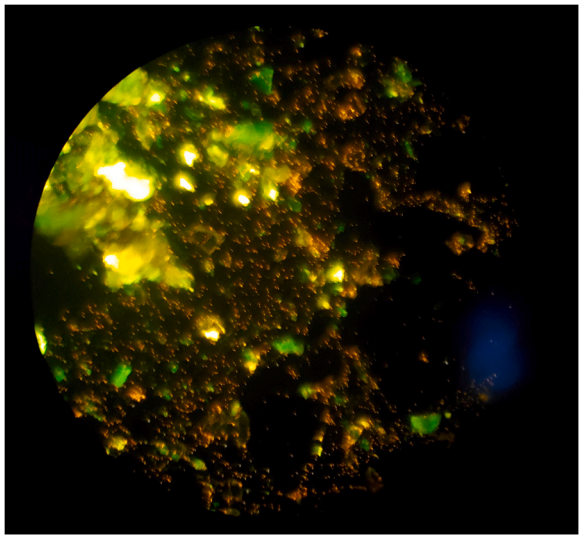

Fig. 2. Abundant acid-fast bacilli visualized with fluorescence microscopy of resected bone (auramine-rhodamine stain, original magnification x1000).

Cultures of the surgical tissue revealed growth of dry white colonies on chocolate agar incubated at 30 °C. There was no growth at any temperature on liquid Middlebrook or on solid Löwenstein-Jensen media, nor on chocolate agar incubated at 37 °C. Matrix-assisted laser desorption/ionization (MALDI) analysis of the cultured organism identified *Mycobacterium haemophilum*. Mycobacterial blood culture was obtained and was negative for growth after 6 weeks. The patient was started on a 3-drug regimen of rifampin, moxifloxacin, and azithromycin until definitive left ankle disarticulation was performed with negative margins demonstrated for both osteomyelitis and acid-fast bacilli.

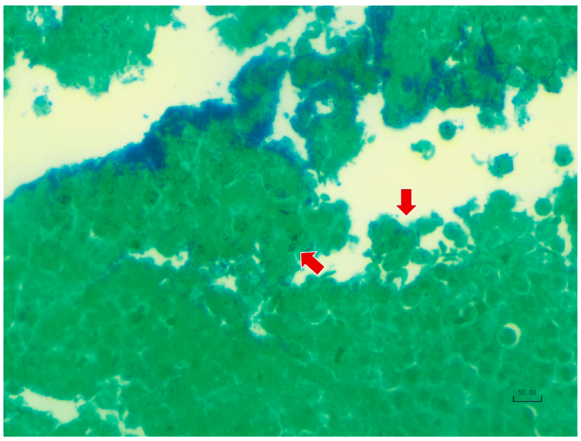

Fig. 3. Heavy burden of slim, rod-shaped bacteria within operative bone specimen, as indicated by red arrows. (Ziehl-Neelsen stain, original magnification x1000).

Discussion

Mycobacterium haemophilum is a slow-growing, aerobic, and fastidious non-tuberculous mycobacteria (NTM) that is recognized as an uncommon opportunistic pathogen worldwide among immunocompromised adults. *M. haemophilum* was first identified in the literature in 1978 in a 51-year-old woman undergoing treatment for Hodgkin's lymphoma who presented with numerous non-healing subcutaneous abscesses of the trunk and extremities. The organism was isolated from cutaneous aspirates and was found to have several unique growth features, notably preferential growth at 30–32 °C and the requirement for iron- or hemin-containing culture media [1]. *M. haemophilum* is not identifiable with conventional Gram staining techniques though it stains strongly acid-fast with Ziehl-Neelsen, Kinyoun, or fluorochrome dyes [2]. The organism appears as short, curved rods under light microscopy and cultured specimens may additionally exhibit cording or clumping (Fig. 4), though visible growth may require up to 8 weeks. A high degree of suspicion must exist to properly isolate the organism in the microbiology lab to accommodate its unique

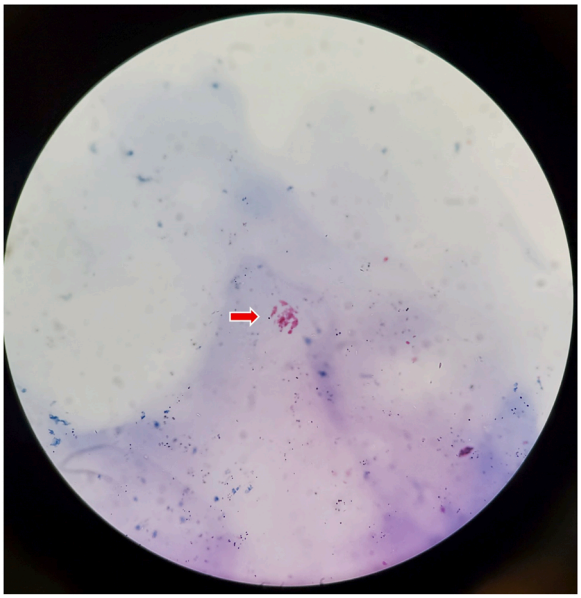

Fig. 4. Ziehl-Neelsen stain of cultured *Mycobacterium haemophilum* specimen demonstrating beaded acid-fast bacilli in a clumped pattern, as indicated by red arrow. (original magnification x1000).

growth requirements.

The classical clinical presentation of *M. haemophilum* in adults involves ulcerating cutaneous infection or musculoskeletal infection of the distal extremities [2–6], likely owing to the organism's predilection for growth at lower temperatures. This pattern mimics that of other cutaneous mycobacteria such as *M. ulcerans* or *M. marinum*. Curiously, the organism is also known to cause sub-acute to chronic cervicofacial lymphadenitis in otherwise healthy immunocompetent children [2,3]. Among immunocompromised adults, the most common predisposing conditions in the literature include hematologic malignancy, solid organ and bone marrow transplantation, and infection with Human Immunodeficiency Virus (HIV). Small observational studies suggest a higher rate of dissemination and central nervous system involvement among patients co-infected with HIV [4]. As is the case with other mycobacterial disease, *M. haemophilum* infection typically develops over a sub-acute to chronic time course, and diagnostic delays are possible if the organism is not immediately suspected as the cause of infection. Our patient experienced a diagnostic delay until worsening laboratory and imaging findings prompted a more invasive approach. Overall, the prevalence of *M. haemophilum* infection is likely underestimated in the literature due to the organism's unique growth requirements and special considerations for culture.

To date, no large-scale clinical trials have characterized the clinical presentations of *M. haemophilum* infection. Much of our understanding of infection stems from case series and isolated case reports, and cases of *M. haemophlium* infection have been reported from all 6 inhabited continents [3]. A single institution case series by Shah et al. from the Memorial Sloan-Kettering Cancer Center in New York, New York examined 23 adult patients with *M. haemophilum* infection from 1990 through 2000. Of the 23 patients described, 14 had undergone bone marrow transplantation, 5 had HIV infection, and 3 had hematologic malignancy. Isolated cutaneous infection was seen in 13 patients and 4 patients had musculoskeletal infection with either septic arthritis or osteomyelitis. An additional 6 patients had pulmonary involvement, with one patient simultaneously experiencing both pulmonary and skin involvement [5]. On average, patients who presented with musculoskeletal manifestations of *M. haemophilum* infection had less underlying immunocompromise compared with those who presented with primarily pulmonary disease (median CD4 cell count 385/μL and 18/μL, respectively), highlighting the crucial importance of cell-mediated immunity in disease pathogenesis. A single institution case series by Tyner et al. from the Mayo Clinic in Rochester, Minnesota similarly examined 10 adult patients with *M. haemophilum* infection from 2000 to 2015. Of these 10 patients, 5 had rheumatologic disorders requiring immunosuppressive therapy, 3 were known to have malignancy, 1 was the recipient of a kidney transplant, and 1 had no known immunocompromising condition. All 10 patients were HIV seronegative, though no laboratory measure of immunocompromise was reported to describe this population. Cutaneous infection was again the leading clinical presentation in this cohort, with 7 patients presenting with skin and soft tissue infection of the distal extremities. One patient experienced concomitant skin and bloodstream infection, and no patients were reported to have pulmonary involvement [6]. Notably two patients, both adults, presented with cervicofacial lymphadenitis.

Non-tuberculous mycobacteria remain a relatively uncommon cause of opportunistic infection in renal transplant recipients, with estimated incidence ranging from 0.16 % to 0.55 % [7]. However, a wide array of clinical manifestations due to *M. haemophlium* has been reported within the renal transplant population. Cutaneous infection remains the most common presentation though there are rare instances reported of pyomyositis [8], dissemination with brain abscess formation [9], and dissemination with graft involvement [10]. Differences in immunosuppressive intensity likely account for the disease heterogeneity in this population.

As is the case with other non-tuberculous mycobacteria, *M. haemophlium* is believed to be ubiquitous within the environment, though the organism's natural habitat is not well characterized. It is postulated that *M. haemophilum* inhabits aquatic environments, and studies examining the presence of mycobacteria in municipal water distribution supplies have demonstrated the presence of *M. haemophilum* in well water systems in the United States [11] as well as within water meter biofilms [12]. We believe our patient acquired infection through nightly Epsom salt soaks of his feet using contaminated municipal tap water, which the patient reported practicing for several years, although our attempts to culture the organism from the vessel used for the soaks were unsuccessful. To the authors' knowledge, our case represents the first reported case of *M. haemophlium* osteomyelitis acquired through such an exposure history. Another unusual feature of our case is the multi-focal nature of the patient's osteomyelitis (Fig. 1) in the absence of disseminated bloodstream infection. Multi-focal hematogenous osteomyelitis is more commonly described in prepubertal children than in adults [13], and we postulate that the patient's foot soaks allowed the mycobacteria to enter via multiple portals of entry in the skin in the absence of systemic bacteremia.

There are currently no standardized treatment guidelines for the management of *M. haemophilum* infections. The American Thoracic Society and Infectious Disease Society of America jointly released a clinical practice guideline for the diagnosis and treatment of NTM diseases, though the authors concede that there is no single recommended treatment regimen or duration for *M. haemophilum* [14]. The organism demonstrates in vitro susceptibility to clarithromycin, ciprofloxacin, clofazimine and rifampin while also demonstrating resistance to isoniazid and ethambutol [3–6]. Anti-mycobacterial drug regimens should be tailored to the individual patient's immunocompromising condition, with special attention paid to drug-drug interactions with either combination anti-retroviral therapy or with common anti-rejection medications. Isolated cutaneous disease due to *M. haemophilum* appears to respond well to shorter durations of therapy (3 – 6 months), while musculoskeletal infections tend to require longer therapy (12 months or more), with or without surgical source control [4]. Our patient was successfully treated with a combination of local debridement and a 3-drug anti-mycobacterial regimen until definitive amputation could be completed.

Conclusion

Mycobacterium haemophilum should be suspected in immunocompromised patients presenting with ulcerating cutaneous or musculoskeletal infections of the distal extremities that do not respond to conventional antibiotics. A high index of suspicion must exist for diagnosing this organism in an immunocompromised host. In our patient on chronic steroid a lack of response in inflammatory markers to targeted anti-bacterial therapy prompted an evaluation for alternative diagnoses or atypical organisms. Treating physicians should confer with the microbiology lab in attempts to isolate *M. haemophilum*, as the organism uniquely grows at lower temperatures and only on iron-containing culture media. Treatment outcomes are generally favorable in the literature with a combination 2- or 3-drug anti-mycobacterial regimen, although the organism exhibits resistance to isoniazid and ethambutol.

Patient consent

Obtained.

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Authorship

BC wrote the first draft of the manuscript and prepared the figures. SM critically reviewed and revised the manuscript. All authors read and

approved the final paper.

Conflicts of interest

None.

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