Mycobacterium haemophilum Osteomyelitis: Case Report and Review of the Literature

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Abstract

Background
Mycobacterium haemophilum is a slow-growing, fastidious, iron-requiring nontuberculous mycobacterial species found ubiquitously in the environment but which has only rarely been associated with human infection. This organism has primarily been implicated as a cause of ulcerating cutaneous or subcutaneous nodular skin lesions, particularly in immunocompromised patients, although infections at extracutaneous sites have also been described. Osteomyelitis, while rarely documented, appears to be an important complication of infection with M. haemophilum.

Case Presentation
We describe a unique case of culture-confirmed M. haemophilum osteomyelitis in an adult woman with polycythemia vera and review the world literature on skeletal infections due to this organism.

Conclusion
Mycobacterium haemophilum is an important but infrequently encountered cause of skeletal infections in immunocompromised patients, often requiring months to years of combined medical and surgical therapy to effect a clinical cure.

Background

Mycobacterium haemophilum osteomyelitis
*Mycobacterium haemophilum* is a slow-growing, fastidious, iron-requiring nontuberculous mycobacterial species found ubiquitously in the environment but which has only rarely been associated with human infection. This organism has primarily been implicated as a cause of ulcerating cutaneous or subcutaneous nodular skin lesions, particularly in immunocompromised patients, although infections at extracutaneous sites have also been described. Osteomyelitis, while rarely documented, appears to be an important complication of infection with *M. haemophilum*. We report a case of *M. haemophilum* osteomyelitis in a patient with polycythemia vera and provide a summary review of the world literature on *M. haemophilum* skeletal infections.

**Case Presentation**

A 56-year-old woman with a 16-year history of polycythemia vera, reasonably controlled with busulfan, presented for medical attention with a history of painful ulcerating nodular skin lesions on her right wrist and right ankle. The lesions were biopsied, with special stains showing the presence of acid-fast bacilli (AFB). She was not aware of any contact with tuberculous individuals, and had no history of exposure to fish tanks. She recalled experiencing minor trauma to her right wrist just prior to the emergence of the nodular lesions. Physical examination revealed tender nodular and erythematous ankle and wrist lesions (3 cm and 1 cm in diameter, respectively), with full thickness skin ulceration. Chest X-ray was normal. While awaiting culture results, she was started on oral clarithromycin, ciprofloxacin, and rifabutin, after which her wrist lesion slowly healed. The ankle lesion did not respond significantly to medical therapy. X-rays demonstrated osteolysis of the distal tibia consistent with osteomyelitis. She developed gastrointestinal intolerance to ciprofloxacin and rifabutin, and was continued on clarithromycin alone. After several weeks, a non-Mycobacterium haemophilum osteomyelitis
tuberculous mycobacterial species confirmed to be *M. haemophilum* was isolated in culture. The isolate was susceptible to clarithromycin and rifabutin but resistant to ciprofloxacin, amikacin, and ethambutol. Re-biopsy of the ankle lesion demonstrated the presence of AFB but no evidence of superinfection with other pathogens. An MRI scan 6 months later demonstrated a significant soft tissue inflammatory mass underlying the ulcer with extension through the cortex of the tibia and into the marrow cavity. After debridement, the ulcer began to granulate and heal over.

**Discussion**

*Mycobacterium haemophilum* is a slow-growing, fastidious, nontuberculous mycobacterial species that was first isolated and described by Sompolinsky in 1978, who recovered the organism from chronic ulcerating subcutaneous lesions in a woman with Hodgkin’s disease [1]. Since then, approximately 100 cases of infection have been described worldwide, with the majority of affected individuals being immunocompromised by virtue of organ or bone marrow transplantation, haematological malignancy, or advanced HIV infection/AIDS [2-10]. In such individuals, the classical clinical presentation has been that of multiple tender ulcerating cutaneous or subcutaneous nodular skin lesions, commonly on the extremities and often overlying joints [2-10]. Occasionally, lesions have been associated with cellulitis or complicated by abscess formation, fistula development, osteomyelitis, septic arthritis, or bacteremia [2-4, 6-9]. Cases of pneumonia, pulmonary nodules, or sinusitis without skin lesions have also been described in both immunocompromised and immunocompetent individuals [2-4, 6-11]. Several cases of localized lymphadenitis, particularly of the cervical, submandibular, and perihilar regions, have been reported in immunocompetent patients, especially children [7, 11, 12].

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The natural habitat and mode of acquisition of *M. haemophilum* are unknown. However, the geographic distribution of *M. haemophilum* is thought to be ubiquitous [6, 7]. Evidence from reported cases points to an environmental reservoir, possibly aquatic, although attempts to recover the organism through environmental sampling have been unsuccessful [7, 13]. A few patients have reported antecedent trauma at the site of infection [9, 13]. Although the pathophysiology of *M. haemophilum* infection is not well understood, cell-mediated immunity appears to play a key role in disease pathogenesis and outcome [8, 9].

In common with most other nontuberculous mycobacterial infections, disease is usually chronic [7]. The organism is difficult to cultivate in the laboratory, and is unique among the mycobacteria in its requirement for iron-containing compounds in growth media [7]. Furthermore, *M. haemophilum* requires low incubation temperatures (30-32°C) for growth [7]. Hence, cases of infection due to *M. haemophilum* are likely under-reported.

*Mycobacterium haemophilum* appears to be the most important cause of atypical mycobacterial skeletal infections in humans [3, 14-24]. At least 20 cases of *M. haemophilum* bone infections have been described to date, with most occurring in patients with advanced HIV disease or bone marrow/solid organ transplants [2-4, 6-9, 14-24]. Infections may involve multiple sites, are frequently associated with septic arthritis and/or overlying cutaneous infection, and usually involve the bones of the foot, ankle, knee, elbow, and fingers [2-4, 6-9, 14-24]. These and other sites may be involved via contiguous spread or hematogenous dissemination from a pulmonary or cutaneous source. Affected patients may or may not report a history of antecedent trauma. Infections of bone typically develop over the course of several weeks. Plain film radiographs and MRI scans often reveal well-marginated osteolysis, cortical bone

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destruction, and adjacent soft tissue inflammation. In a 3-year review of atypical mycobacterial skeletal infections in 25 HIV-infected patients, *M. haemophilum* accounted for 44% (11/25) of cases, followed by infection with *M. kansasi* and *M. avium-intracellulare* [3] A study from January 1989 to September 1991 at seven metropolitan hospitals in New York City identified 13 patients with culture-confirmed *M. haemophilum* infections (11 with HIV infection and 2 with bone marrow transplants), of which 6 had osteomyelitis [9]. While our case may be the first report of *M. haemophilum* osteomyelitis in a patient with polycythemia vera, our patient’s predisposition to infection was likely a result of myelosuppression from long-term busulfan therapy. A case of fatal disseminated non-*M. haemophilum* atypical mycobacterial infection was reported in a woman with pulmonary fibrosis secondary to long-term busulfan use [25].

Most strains of *M. haemophilum* demonstrate in-vitro susceptibility to ciprofloxacin, clarithromycin, rifamycins, and clofazimine [4, 5, 7, 10, 26]. Isolates are usually resistant to isoniazid, ethambutol, and pyrazinamide, while susceptibility to doxycycline, minocycline, amikacin, and para-aminosalicylic acid is variable [4, 5, 7, 10, 26]. Treatment for osteomyelitis is usually prolonged, often several months to years in duration, but should be guided by the patient’s underlying condition and clinical response. Combinations of drugs, including ciprofloxacin, clarithromycin, and rifampin have been used successfully for treatment of osteomyelitis or localized skin and soft tissue infection [2-4, 7-10, 18]. Patients with localized disease usually respond favorably to treatment, although deaths have been reported, especially for disseminated infection [4, 5, 7, 8, 10]. Improvement of immune function during the course of disease also appears to improve outcome [6]. After one year of follow-up, our patient’s ankle lesion had completely epithelialized, aside from the development of Mycobacterium haemophilum osteomyelitis
of a small intermittently draining sinus. Repeat MRI another 6 months later demonstrated resolution of the original soft tissue inflammatory mass but without evidence of bony healing. Her isolate was susceptible to clarithromycin and rifamcyins only. She improved after 2 years of clarithromycin therapy, with plans to continue therapy indefinitely until there was radiologic evidence of bony healing, although she eventually died of transformation to acute leukemia.

**Conclusions**

*M. haemophilum* is a clinically significant mycobacterial species with a predilection for causing skeletal infection in immunocompromised individuals. In the appropriate clinical setting, *M. haemophilum* skeletal infection should be considered in the differential diagnosis of immunocompromised patient presenting with nodular or ulcerative skin lesions in conjunction radiographic evidence of adjacent bone destruction, especially if tissue biopsies reveal the presence of AFB.

**Competing interests**

The authors declare that they have no competing interests.

**Authors' contributions**

RR was directly involved in the patient’s care. SE was the laboratory physician involved in the patient’s care. SE performed the literature review. Both authors wrote the manuscript.

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While the patient was alive, informed verbal consent was obtained to publish this report.

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