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Case Report

Identification of Mycobacterium marinum in subcutaneous abscesses of an infected patient's foot

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Abstract

Introduction: *Mycobacterium marinum* is a well-known pathogenic non-tuberculous mycobacterium for skin and soft tissue infections. Infection, often presenting as superficial lesions, is seen after exposure of skin abrasions to contaminated water or infected fish and is known as "swimming pool" or "fish tank" granuloma. This study reported a case of *M. marinum* infection in subcutaneous abscesses of a patient's foot.

Methodology: A diagnosis of *M. marinum* infection was established with the help of tissue biopsy, culture, matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) and molecular analysis.

Results: The patient was diagnosed with *M. marinum* infection in his left foot and received appropriate antibiotic treatment with the desired effect.

Conclusions: In many parts of the developing world, *M. marinum* infections may remain undiagnosed due to limited symptoms, as well as the lack of medical services and laboratory facilities. Key diagnostic elements for *M. marinum* infections include a high index of suspicion raised by chronic lesions, poor response to conventional treatments, a properly obtained exposure history, culture, and microorganism identification. This study provides some references and suggestions for the clinical characteristics, diagnosis, treatment and prevention of *M. marinum* infection.

Key words: *Mycobacterium marinum*; MALDI-TOF; 16S rRNA; *hsp65*.

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Introduction

Mycobacterium marinum is a slow-growing, non-tuberculous mycobacterium that affects more than 200 species of freshwater and marine fish, spanning a broad area from the subarctic to the tropical [1,2]. It is considered as the most important fish pathogen and a great threat to the aquatic industry. The species *M. marinum* has also been found to cause infections in humans that range in severity from simple cutaneous lesions to debilitating disseminated infections [3].

The first human skin infection reported in 1951 occurred in people who swam in contaminated swimming pools after *M. marinum* was originally discovered on saltwater fish in the Philadelphia Aquarium in 1926 [4]. After a large outbreak associated with swimming pools occurred, *M. marinum* infection was initially called swimming pool granuloma. The majority of cases were found in fishermen and aquarium owners following the widespread use of chlorine in swimming pools, leading to the emergence of the term "fish tank granuloma" [5]. In general, there are several groups of individuals at risk, including fishermen and those who work professionally with fish and seafood (including chefs, fishmongers, and oyster shuckers), as well as fish enthusiasts and water sports enthusiasts [6].

The genome of *M. marinum* has been sequenced and assembled in 2008 [7]. Based on a phylogenetic analysis that included additional mycobacterial species, it was revealed that *M. marinum* shares the closest phylogenetic relationship with *M. ulcerans*, followed by *M. tuberculosis* [6]. Infections with *M. marinum* are rare in humans, although solid epidemiological data remain relatively limited. During the ten years covered by a retrospective study conducted at the largest dermatological referral center in Hong Kong, only 17

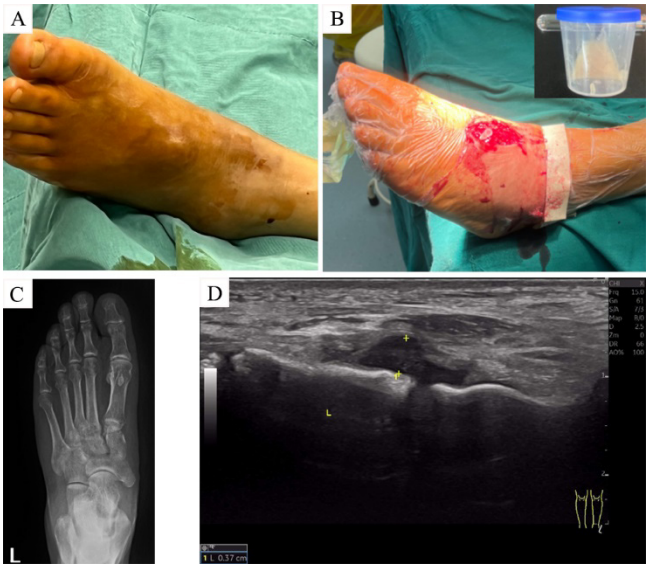
new patients with *M. marinum* infections were identified, which equated to less than 0.005% of the 345,394 new patients [8].

According to one study, the median incubation period for *M. marinum* infections was 21 days [9]. There have been reports of cases where skin lesions have persisted for more than two decades in the literature [10]. In many parts of the developing world, *M. marinum* infections may remain undiagnosed due to limited symptoms, as well as the lack of medical services and laboratory facilities. This study reports a case of *M. marinum* infection and provides some suggestions for the clinical characteristics, diagnosis, treatment and prevention of *M. marinum* infection.

Case Presentation

The 59-year-old man presented with a 6-month history of pain in his left foot back and a 5-month history of subcutaneous nodules. The subcutaneous nodule gradually increases from the initial 0.5 cm × 0.5 cm, with obvious tenderness, no redness or swelling. When the patient was admitted to the hospital on July 13, 2022, there were no abnormalities in the routine blood tests except a slightly high white blood cell count (9.96×10^9/L). The patient's foot condition at the time of admission, X-ray and ultrasound before surgery are shown in Figure 1. The medial, intermediate, and lateral cuneiform bones of the left foot were destroyed, and necrotic bone fragments could be seen at the edge of the medial cuneiform bone. There is a decrease in the density of the bone marrow cavity at the base of the second metatarsal bone, which might indicate osteomyelitis. Since the onset of the disease, the patient had no fever, night sweats, weight loss, as well as no eating and sleeping problems. The patient denied a history of infectious diseases such as tuberculosis, viral hepatitis, clonorchiasis, and schistosomiasis. He denied a history of chronic diseases such as chronic bronchitis, hypertension, coronary heart disease, kidney disease, and diabetes. He had no food allergy and was allergic to sulfonamide antibiotics. The patient is a driver who likes swimming. He has never raised fish at home. Five years ago, he often swam in the shallow sea area, but he did not remember whether his feet were injured when swimming. The patient was diagnosed with vasculitis a year ago and had been taking 10 mg of methylprednisolone orally every day.

Figure 1. A. the lesion of the patient's left foot back; **B.** the pus extracted from the lesion during operation; **C.** X-ray and **D.** ultrasound images of the patient's left foot back before therapy.



The lesion of the patient's left foot back was excised and sent for culture and histological examination. Histology revealed chronic inflammatory granulation tissue and non-caseating giant cell granulomata (Figure 2). The pus extracted from the lesion was directly stained with Gram stain and acid-fast stain in time. Only four acid-fast bacilli were found on the whole slide by acid-fast stain, as shown in Figure 3D. Some pus was inoculated onto the blood plate. On the fifth day, the inoculation ring was used to smear the surface layer on the blood plate and then smeared on the slide for acid-

Figure 2. Histopathologic section of tissue from a patient with a *M. marinum* infection. **A.** a small piece of tissue at the lesion; **B and C.** the lesion shows granulomatous infiltrate with epithelioid and giant cells (100x magnification).

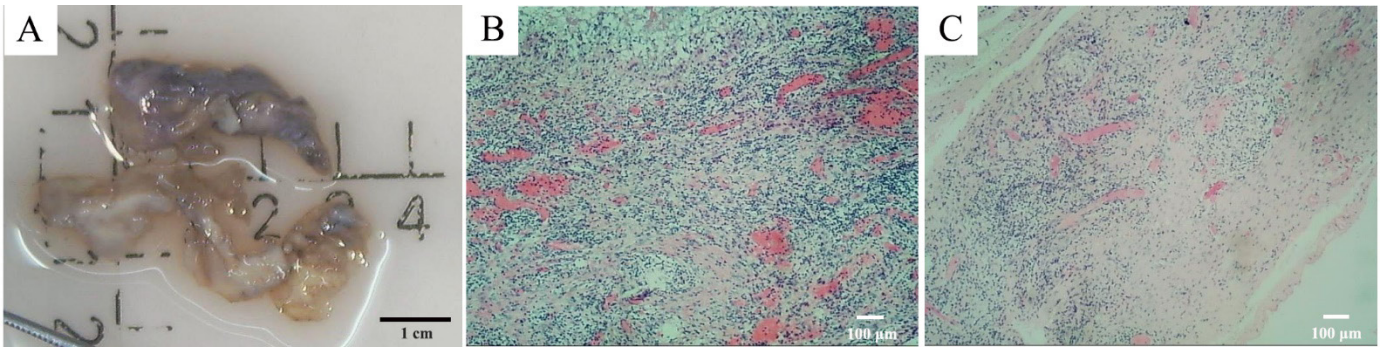
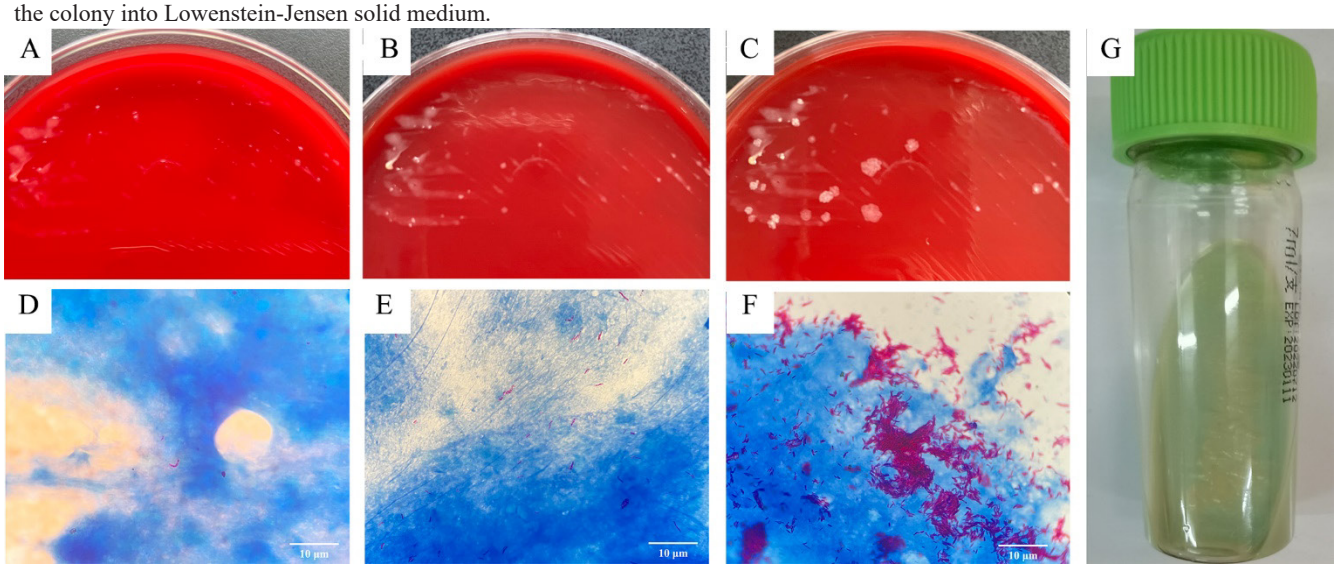


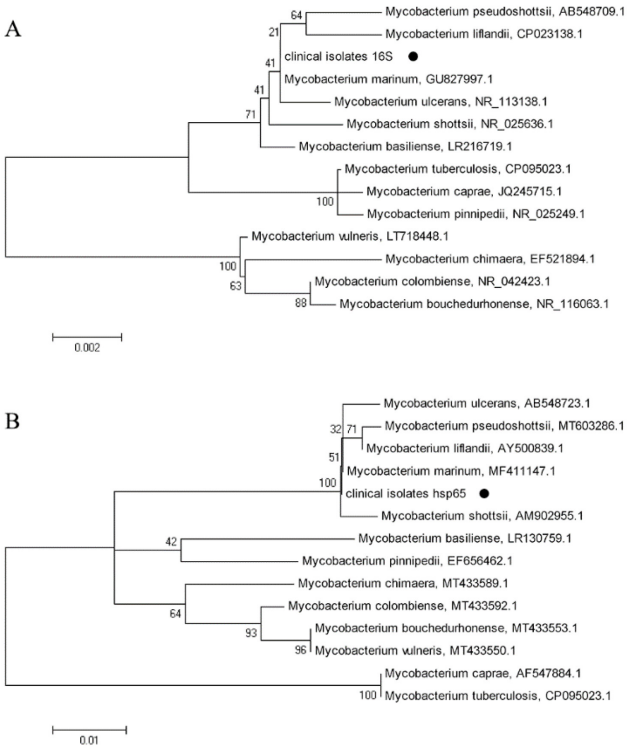
Figure 3. A, B and C. colony morphology results of pus cultured on blood plate for 5 days, 8 days and 10 days, respectively; **D.** the pus extracted from the lesion was directly stained with acid-fast stain in time (1000x magnification); **E and F.** acid-fast staining results (1000x magnification) of pus cultured on blood plate for 5 days and 8 days, respectively; **G.** colony morphology one day after directly inoculating the colony into Lowenstein-Jensen solid medium.



fast staining. Although there was no visible colony formation on the surface (Figure 3A), many acid-fast bacteria could be found in the oil lens (Figure 3E). On the eighth day, colonies visible to the naked eye appeared as shown in Figure 3B. Pure colonies were selected for acid-fast staining. The results are shown in Figure 3F. On the tenth day, very typical and dry flat colonies can be seen on the blood plate (Figure 3C). When we inoculated the colonies into a Lowenstein-Jensen solid medium, the colonies were typically smooth, white when the media was kept in the dark, and yellow after exposure to light (Figure 3G). However, the aerobic culture bottle and anaerobic culture bottle containing the pus were tested negative by the blood culture instrument after 5 days of culture.

The results of mass spectrometry are dependent on the quantity and accuracy of the database; we identified the isolate by Vitek MS as *M. marinum* based on a confidence level of 99.9%. When additional molecular identification via polymerase chain reaction (PCR) amplification of the 16S rRNA gene – universal primers: 27F (5'-AGAGTTTGATCMTGGCTCAG-3') and 1492R (5'-GGTTACCTTGTTACGACTT-3') – was performed, the clinical isolate (GenBank: OQ693599.1) exhibited a 16S rRNA similarity of 100% with *Mycobacterium sp.* (GenBank: OM691430.1) and *M. marinum* (GenBank: GU827997.1). Molecular identification of the *hsp*65 gene – forward primer (5'-ACCAACGATGGTGTGTCCAT-3') and reverse primer (5'-CTTGTCGAACCGCATACCCT-3') – which facilitates the precise identification of *Mycobacterium sp.*, was performed. The clinical isolate (GenBank: OQ801488.1) exhibited a *hsp*65 similarity of 100% with *M. marinum* (GenBank: MF411147.1). Multiple sequence alignments were created from the same gene of the clinical strain we collected and other mycobacteria in the NCBI database. Phylogenetic tree (Figure 4) of 14 nucleotide sequences were constructed

Figure 4. A phylogenetic tree of the clinical isolate and 13 other Mycobacterium bacteria form GenBank was constructed with 16S rRNA (A) and hsp65 gene (B).



with the MEGA software version 7.0.26. The clinical isolate strain clustered most closely with *M. marinum* GU827997.1 and MF411147.1. Therefore, the clinical isolate strain was confidently identified as *M. marinum*.

The patient received a combined treatment for six months composed of ethambutol 400 mg three times a day for three months and rifampicin 300 mg twice daily for six months. After the first skin incision and drainage at admission, topical treatment was not performed again. The abscess disappeared 6 months after drug use, with no relapse to date.

Discussion

As an opportunistic, photochromogenic, non-tuberculous species of bacteria, *M. marinum* is the most commonly affecting non-tuberculous mycobacterium in humans, along with the members of *Mycobacterium avium* complex [11]. Infections with *M. marinum* can be classified into four clinical categories (type I–type IV) [12]. Type I infection with *M. marinum* is often associated with immunocompetent patients presenting with a single or limited number (1–3 lesions) of superficial cutaneous infections (ulcerated, crusted, or verrucous plaques or nodules). Type II infection with *M. marinum* is identified by the presence of multiple (> 3) lesions in a sporotrichoid distribution pattern, or by the presence of inflammatory nodules, abscesses, and granulomas in a patient with an immunosuppressed state. There is a possibility of developing nodular lymphangitis from this sporotrichoid infection after distal inoculation [13]. Type III infection with *M. marinum* is characterized by deep infections with or without skin involvement, including tenosynovitis, arthritis, bursitis, and/or osteomyelitis. Type IV infection with *M. marinum* is characterized by disseminated infection with lung disease and other systemic manifestations. The incidence of bacteraemia is extremely low, although it may occur in patients with severe immuno-compromised states [12,14].

Due to the insidious nature of the presentation and the lack of specificity of the symptoms, a clinical diagnosis can be challenging. It is common for the diagnosis to be delayed if key historical information is not obtained, such as fish exposure [9]. When diagnosing *M. marinum* infections, it is important to have a high index of suspicion based on negative bacterial tissue cultures, an appropriate exposure history, a poor response to conventional antibiotic treatment, and knowledge of the organism's laboratory growth characteristics [15]. If a patient exhibits typical cutaneous manifestations and has been exposed to an aquatic environment such as a fish tank, the diagnosis of *M. marinum* infection should be considered on clinical grounds. The patient in this case was at risk of being exposed to a potentially polluted aquatic environment, but it is not certain that it has been latent infection for several years. It might have been infected unknowingly while swimming at the seaside five years ago, and its symptoms might have appeared after taking immunosuppressants a year ago. The diagnosis remains largely presumptive in practice, based on clinicohistological features and the response to appropriate antimicrobial treatment, regardless of culture results [16]. However, the diagnosis should be confirmed by histological and microbiological examinations. In this case, the histologic examination of biopsy specimens showed granulomatous inflammation and fibrosis. In most cases, Histopathological examinations revealed a mixture of lymphocytes, macrophages, giant cells, and polymorphonuclear leukocytes [17]. It is necessary to isolate and identify the organism in order to make a definite diagnosis. Molecular identification allows the early detection of the organism from a biopsy specimen by using PCR. The use of this technique may prove valuable and may ultimately replace conventional methods as the test of choice for rapid diagnosis and species identification of nontuberculous infections [18]. There is consensus that the conserved genes or DNA regions (*hsp*65, *gyr*A, *rpo*B, and 16S-23S internal transcribed spacer) allow molecular identification of mycobacterial species [19]. Here are some suggestions for the diagnosis of *M. marinum* infection: (i) inquire about possible exposure history. For example, “Do you keep fish at home? How to clean fish tank?”; (ii) sample the lesion for bacterial culture or sequencing analysis; (iii) inform the laboratory that the lesion may be infected with *M. marinum*; and (iv) incubate at 30°C for several weeks in addition to 37°C until smooth photochromogenic colonies appear.

There is currently no consensus on the optimal treatment of *M. marinum* infection. Several antibiotics have been shown to be effective against *M. marinum*, including rifampin, rifabutin, ethambutol, clarithromycin, sulfonamides, trimethoprim/sulfamethoxazole, doxycycline, and minocycline [20,21]. Various authors consider susceptibility testing not to be recommended on a routine basis, mainly because *in vitro* results do not necessarily indicate *in vivo* effectiveness, and the risk of acquired resistance to widely used antimicrobials is minimal for *M. marinum*, which is particularly susceptible to these drugs [22]. So, it is not necessary to conduct a routine susceptibility test other than relapsed

cases as recommended for atypical mycobacteria [23]. Among the most commonly used combinations in the literature are clarithromycin and rifampin, clarithromycin and ethambutol, or rifampin and ethambutol. It is recommended to treat systemic infections with a combination of three or more drugs [24]. The current researches indicate that specific gene mutations have an impact on the drug resistance levels of both tuberculosis and non-tuberculosis mycobacteria (NTM) [25]. Therefore, it would be advisable to identify the relevant resistance genes in NTM (including *M. marinum*) for guiding drug administration. In cases of tissue necrosis and septic arthritis, the intervention may facilitate the effects of antibiotics as an adjunctive treatment [26]. There have been reports of cryotherapy, laser and photodynamic therapy being effective treatment options [27], but few studies have evaluated their effectiveness. There is a general recommendation to continue antibiotic treatment for at least two months following the healing of the lesions, especially if the infection has progressed to deeper tissues.

M. marinum infection does not transmit from person to person, so preventing inoculation from the environment is the primary strategy for eliminating the disease. There is no doubt that individual prevention is the most effective line of defense for anyone who is involved in aquaria or who works or recreations in a marine environment. Several simple recommendations should be widely available to the public, such as measures for hand protection and hygiene and advice on fish tank and aquarium maintenance (i) Wear gloves when cleaning fish tanks and handling aquatic products. (ii) Use bandages and avoid swimming if the open wounds are exposed to potentially contaminated water or infected fish. (iii) Always thoroughly clean your hands after contacting aquarium water and components. (iv) Be careful not to swallow aquarium water when siphoning water [28]. (v) A UV germicide lamp is an effective tool to treat aquarium water for killing mycobacteria as long as it is used in clean conditions at the appropriate flow rate [29]. (vi) Do not transfer tank filters or fishes into the bath or basin that is used for humans, unless it is thoroughly cleaned with sodium hypochlorite [30]. (vii) People with high exposure risk should be educated to take effective preventive measures and recognize signs of *M. marinum* infection in fishes and humans, so that they can inform the medical staff, which will expedite the diagnosis.

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Ethics approval and consent to participate

This work was approved by the Ethics Committee of Shenzhen Qianhai Shekou Free Trade Zone Hospital. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Authors' Contributions

Yong Wei, Jiachun Zhang, and Xuli Xin contributed equally to this work.

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