Mycobacterium marinum Infection of the Hand in an Immunocompromised Aquarium Hobbyist

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ABSTRACT *M. marinum*, a nontuberculous mycobacterium, is a rare human pathogen widely distributed in the aquatic environment. In the previous century, epidemics took place due to inadequately chlorinated swimming pool water. Nowadays the majority of infections are acquired through contact of previously damaged skin with contaminated fish tank water. We present a case of *M. marinum* infection of the hand in an aquarium hobbyist which stayed unrecognized for 2 years. After confirming the correct diagnosis, the patient was successfully treated with a regiment containing clarithromycin and rifampicin. The aim of this paper is to raise the awareness of the possibility of *M. marinum* infection when encountered with non-healing nodular/verrucous/ulcerative lesions of the extremities.

KEY WORDS: *Mycobacterium marinum*, skin infection, aquarium, clarithromycin, rifampicin

INTRODUCTION

Mycobacterium marinum, a nontuberculous mycobacterium, is a rare and sometimes forgotten cause of chronic granulomatous skin disease (1). It is found in aquatic environments worldwide, typically causing chronic systemic infections in fish. Transmission to humans occurs through contact of previously damaged skin with contaminated, predominately still water (aquariums, inadequately chlorinated swimming pools), through injuries inflicted by fish hooks, or through cuts while handling raw fish ([2-4). Granulomatous skin lesions are seen at the entrance site of *M. marinum*, thus the lesions are predominately located on the hands and forearms. Diagnosis is established by the culture of *Mycobacterium marinum* from a tissue biopsy specimen (3). For less complicated lesions, 3-4 months of dual antimicrobial therapy is usually sufficient (3, 5).

CASE REPORT

A 43-year-old male Caucasian patient was referred to our Department due to a non-healing nodular/verrucous lesion on the dorsum of his left hand. The patient first noticed three erythematous nodules on his left, non-dominant hand and forearm two years prior to the first visit. Lesions on the left forearm healed spontaneously during a one-month period, but the one on the dorsum of his left hand slowly expanded. He could not remember any previous trauma. The lesion caused some psychological concern, but otherwise the patient was symptom-free.

His medical history was significant for splenectomy due to spherocytosis, which was preformed 4 years before the onset of skin lesions. He was otherwise healthy and in good general condition. He did not have a history of tuberculosis. His family history was negative for skin diseases. He possessed a couple

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of aquariums in his apartment, which he regularly cleaned without wearing protective gloves. The history for contact with other animals was negative. He was not taking any medications at the time of presentation.

He was treated by a general practitioner and by a dermatologist with a topical antibiotic, antimycotic, and corticosteroid therapy along with a short course of peroral antibiotic (azithromycin) with further progression of the lesion. Two biopsies were performed at the local hospital. The first pathological examination of the tissue sample described it as containing chronic inflammation. Due to neutrophilic microabscesses found in the epidermis, periodic acid–Schiff (PAS) staining was performed and came out negative. The second sample, taken 8 months, later showed chronic inflammation with pseudopapillomatous hyperplasia. No granuloma formations were found. Repeated mycological examinations were native and culture negative. Scrapings or tissue specimen for microbiological examination were not taken. Epicutaneous testing was performed, and thimerosal positivity was confirmed.

At the time of presentation at our Department, dermatological examination revealed a single sharply circumcised nodular to verrucous erythematous to violaceus plaque on the dorsum of the left hand. There was no regional lymphadenopathy (Figure 1).

Tissue scrapings were taken for mycological analysis. Two tissue biopsies were performed for histological examination and culture. Routine laboratory chemistry and chest radiography were within normal limits. Syphilis serology (VDRL and TPHA) was negative. Tuberculin skin test was ›15 mm in diameter. Patient history was positive for *bacilli Calmette-Guérin* (BCG) immunization. The Quantiferon test was performed. After obtaining a positive result, multiple sputum and urine samples were examined for the presence of acid-fast bacilli. Sputum samples were examined using smear microscopy and mycobacterial culture; urine samples were examined using mycobacterial culture. All sputum smears and sputum and urine cultures were negative.

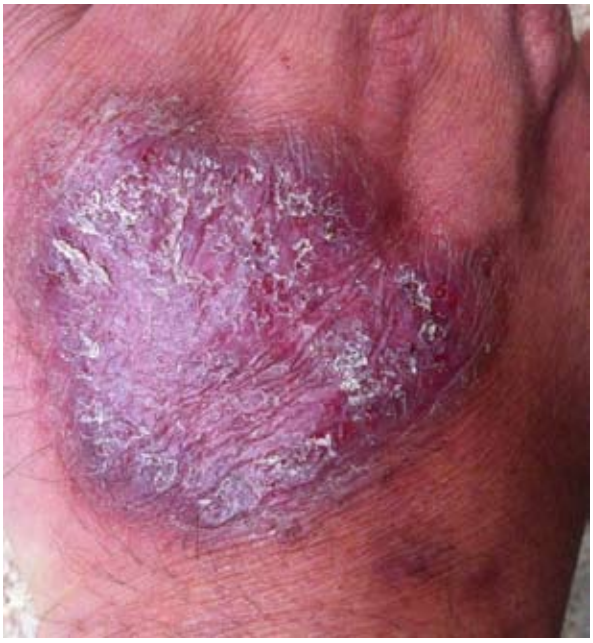

Figure 1. Clinical findings in our patient at admission: sharply circumcised verrucous violaceus plaque on the dorsum of the left hand.

Histopathological examination showed marked epithelial acanthosis, dermal fibrosis, and with multiple small histiocytic and neutrophilic granulomas. Multinucleated giant cells were also observed. Caseous necrosis was not present. Acid-fast bacilli (AFB) staining was negative (Figure 2, A, B).

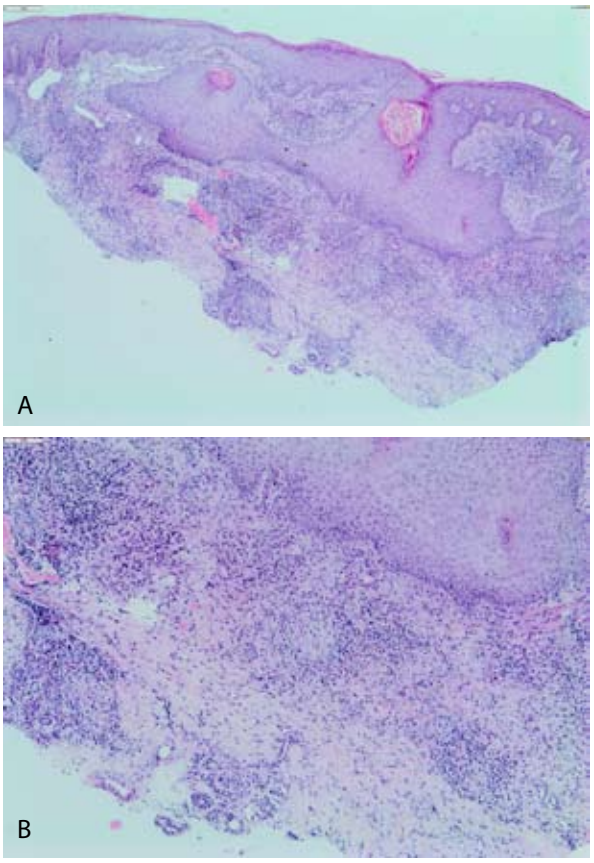

Figure 2. (A) There is marked acanthosis-like pseudoepitheliomatous hyperplasia. Multiple small and poorly formed granulomas are present in the upper dermis with intervening chronic inflammatory cells (hematoxylin and eosin stain, original magnification ×40). (B) Granulomas are better seen at higher magnification (hematoxylin and eosin stain, original magnification ×80).

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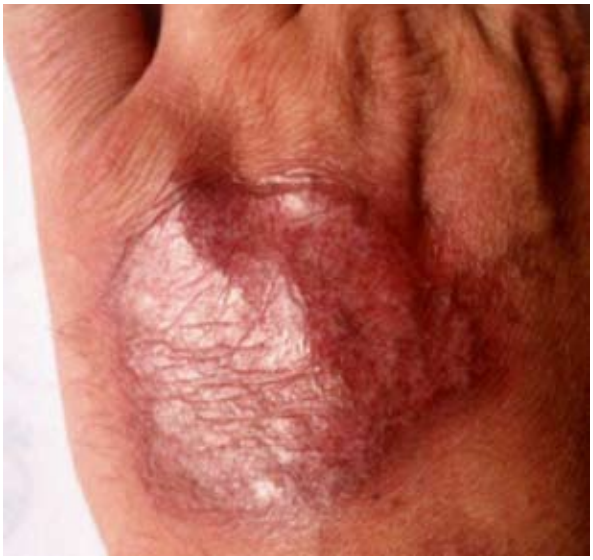

Figure 3. Three months after completion of dual antimicrobial therapy: atrophy, residual hyperpigmentation, and slight scaring is present.

The tissue specimen was cultured for mycobacteria on Loewenstein-Jensen at 31°C and 37°C and liquid MGIT media. Growth occurred after 10 days at 31°C, and there was no growth at 37°C. Colonies were cream in color and turned yellow when exposed to light. Biochemical testing showed positive reactions for urease, Tween hydrolysis, and pyrazinamidase activity. Negative tests included nitrate reduction, arylsulfatase (3-day test), and heat-stable catalase at 68°C. The results of the biochemical tests were indicative of *M. marinum*. The final identification was done with the hybridization GenoType Mycobacterium CM/AS test (Hain Lifescience, Nehren, Germany).

Fungal and other standard bacterial tissue cultures were negative.

Before culture results were available, *M. marinum* infection was the presumed cause, and combined dual therapy was initiated. It consisted of orally administrated clarithromycin 500 mg twice a day plus rifampicin 600 mg once a day. The patient reported mild nausea and headache which were tolerable. No laboratory test abnormalities were observed. After 6 weeks of therapy, the lesion completely resolved leaving an atrophic and heavily hyperpigmented scar. Therapy was continued for a total duration of 3 and a half months. Atrophy was still present 6 months after the completion of therapy, while hyperpigmentation was less obvious (Figure 3).

DISCUSSION

M. marinum, a nontuberculous mycobacterium, was first identified as a human pathogen in 1951 when it was isolated from granulomatous skin lesions in patients from Sweden (6). *M. marinum* is widely distributed in aquatic environments such as natural water (still or stagnant, salty or fresh), fish tanks, and swimming pools. Transmission occurs through inoculation of *M. marinum* through small, sometimes even unnoticed breaks in the skin (2-4). In previous decades, outbreaks were mostly due to inadequate chlorination of swimming pool water; thus the name "swimming pool" granuloma. Nowadays the infection is most commonly acquired while cleaning aquariums, as was the case with our patient who cleaned his aquarium without wearing protective gloves. Less commonly, infection occurs after fish hook injuries or by direct contact of previously damaged skin with raw fish, oysters, or other spiny sea animals (2-4,7). The incubation period varies, usually from 2 to 4 weeks, but long incubation periods up to 270 days have been reported (7). Both immunocompetent and immunocompromised persons are prone to infection. Our patient was immunocompromised due to splenectomy. Most often one, seldom multiple, red-to-violaceous papules or nodules are seen at the site of inoculation, that later evolve into a verrucous plaque with the possibility of ulceration. Skin lesions are usually located on the upper extremities. Less common are abscesses, sporotrichoid spread, lymphangitis, tenosynovitis, septic arthritis, bursitis, or osteomyelitis occurs (8). Dissemination of infections is rarely seen, mostly in already immunocompromised patients, but cases of dissemination were reported due to misdiagnosis and incorrect treatment (primarily with intralesional and or peroral corticosteroid therapy) (9-11).

Diagnosis is based on positive risk factors (aquarists, fishermen, anglers, participants in waterborne activities, history of injury while handling fish or oysters), the clinical picture, pathologic examination of tissue, acid-fast bacilli staining, culture, and polymerase chain reaction (PCR) testing if available (3).

A delay in diagnosis is more a rule than an exception and usually ranges from 3 to 8 months (12). In some cases, the infection stays unrecognized for years (13). There was a two-year delay in the case presented here and was probably due to the lack of a detailed exposure history, two unspecific biopsy results, a relatively indolent course, and low awareness of the possibility of *M. marinum* infection among physicians.

The possibility of unspecific histopathological findings usually showing acute or chronic inflammation without granulomatous inflammation along with negative acid fast staining can lead physicians away from the correct diagnosis, as in our case (14).

The delay in diagnosis is further enhanced by

technical difficulties (optimal temperature for mycobacterial growth, adequate tissue sampling, previous treatment with antibiotics) occurring during microbiological confirmation of the organism. Tissue biopsy is the most sensitive means of obtaining a sample for culture (3). Since low temperature is required for the growth of *M. marinum*, it is important to notify the microbiological laboratory to ensure appropriate incubation temperature. To avoid any misunderstanding, we informed our laboratory both in writing and verbally. Our patient was advised by a dermatologist to receive empirical antimicrobial therapy, ciprofloxacin for 10 days, just prior to tissue biopsy. As quinolones can interfere with *M. marinum* culture growth, antimicrobial therapy prior to taking biopsy specimen for culture should be avoided.

Nonspecific results of histopathological examination, negative acid fast stain, and negative culture results should be taken with caution since they do not exclude *M. marinum* infection (2). In appropriate settings, such as positive aquatic exposure and nonhealing popular/nodular/verrucous skin lesions of the extremities with strong clinical suspicion, empirical therapy should be started to avoid local complications and possible dissemination (15). Unjustified therapeutic attempts such as intralesional and systemic corticosteroid therapy should be avoided (12).

Patients with *M. marinum* infection often present positive tuberculin skin tests due to cross reactions. Quantiferon-TB Gold and enzyme-linked immunospot assay may also be positive in *M. marinum* infections. After obtaining both positive purified protein derivative (PPD) and Quantiferon test results, we conducted further evaluation to exclude latent tuberculosis, keeping in mind that positive results are probably due to *M. marinum* infection. PPD positivity may be due *M. marinum* infection and in such cases should not be the sole indication for starting treatment for latent tuberculosis (2,15).

Due to the rarity of the infection, there are no clinical trials to guide optimal management. Therapeutic decisions are made based on known drug susceptibility testing results, outcomes reported in case series and case reports, and personal physician experience. Topical treatment is completely ineffective as the sole treatment (16). Dual drug therapy seems appropriate for most cutaneous infections (3,5,15). Clarithromycin in combination with ethambutol or rifampicin is a reliable combination that provides an optimal combination of efficacy and tolerability (13,17). Azithromycin seems to be a reasonable alternative to clarithromycin (3). There are case series that report successful single drug therapy for minimal cutaneous infection, primarily using minocycline and secondly doxycycline (1,18,19). A recent study has demonstrated that clarithromycin monotherapy can be a successful treatment option for noninvasive cutaneous infection (20). Even though cases and case series of successful monotherapy have been described, some authors believe it should be avoided because of the unreliability of susceptibility testing and the possibility of emerging resistance coupled with treatment failure (2). The recommended duration of therapy is 1 to 2 months after complete resolution of lesions. Typically, a course of 3 to 4 months of pharmacotherapy is needed (3,5,17). A longer duration of therapy is often required for deeper infections, sometimes with the addition of a third antimicrobial agent along with other measures, primarily surgical intervention (2,3,5,17).

Drug susceptibility testing is not routinely recommended and was not performed in our case due to rapid therapy response. It should be considered in patients who do not respond to therapy and remain culture-positive after 3 months of therapy (3).

In present case, even though the epidemiological history and clinical findings were very suggestive of *M. marinum* infection, no suspicions towards the correct diagnosis were raised among physicians. Misdiagnosis was a consequence of various circumstances: insufficient correlation of epidemiological and clinical data, two unspecific biopsy results, and lack of awareness of the possibility of *M. marinum* infection.

CONCLUSION

The goal of this paper was to raise awareness of general practitioners and especially dermatologists of the possibility of *M. marinum* infection when encountering non-healing nodular, verrucous, or ulcerative skin lesions. The key diagnostic elements for *M. marinum* infections are a high index of suspicion, poor response to conventional antibiotic therapy, and positive aquatic exposure. The proper diagnostic algorithm should be followed. Adequate knowledge of the laboratory growth characteristics of the organism is important. To avoid further complications and possible dissemination, adequate antimicrobial and/or antimycobacterial therapy should be promptly started. Appropriate preventive measures, such as wearing protective waterproof gloves while cleaning fish tanks, can decrease the possibility of transmission of *M. marinum* infection. To avoid misdiagnosis and mistreatment, *M. marinum* infection should always be included in the differential diagnosis of nonhealing lesions on the extremities.

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