Delayed diagnosis of Mycobacterium marinum infection: A case report and review of the literature

M. Dolenc-Voljč and M. Žolnir-Dovč

SUMMARY

Mycobacterium marinum **infection is the most common atypical skin mycobacterial infection of increasing importance. It results from skin injury and contact with contaminated aquarium water, fish, or shellfish; it is only rarely related to swimming pool sources nowadays. Diagnosis should be confirmed by isolation and identification of the organism; however, this gold standard is difficult to achieve in practice. Therefore, the diagnosis is primarily based on clinical examination, histopathology, and response to therapy. Awareness of this infection is still low and diagnosis often delayed, as presented in this case of a young immunocompetent patient with *M. marinum* infection of a chronic course. The reasons for the delay in diagnosis are discussed and current diagnostic and treatment recommendations are reviewed.**

KEY WORDS

***Mycobacterium marinum*, skin infection, swimming pool granuloma, diagnosis, treatment**

Introduction

Atypical mycobacteria are a group of environmental saprophytes occurring in fresh and salt water, soil, and some plants and animals worldwide. They are considered to be facultative pathogens for humans, entering the body via inhalation or ingestion, or through the skin. Skin infections are mainly a result of previous skin injuries. In European countries, *Mycobacterium marinum* is the most common atypical mycobacteria isolated from the skin, whereas in tropical areas *M. ulcerans* is most commonly observed (1, 2).

The first case of *M. marinum* skin infection was reported in 1951 (1). From 1966 to 1996, about 650 cases were reported worldwide, as determined by searching the Medline database (3). The same source reveals that at least 200 additional cases of this infection in humans have been described since 1996. Cutaneous infections with *M. marinum* do not occur often; therefore, they are rarely seen in everyday dermatological practice. They are mainly aquarium-related or the result of fish or shellfish injuries; swimming pools and other freshwater sources seldom contribute to their occurrence (1, 3). The infections remain localized in immunocompetent individuals, whereas immunocompromised patients often suffer from disseminated and more invasive skin infections. Infections caused by atypical mycobacteria are becoming increasingly significant in both immunocompromised and immunocompetent hosts (1, 2).

Here we present the case of a 16-year-old boy with *M. marinum* skin infection with delay in diagnosis and a chronic course. Current diagnostic and treatment recommendations are also reviewed.

Case report

A 16-year-old boy noticed a tender erythematous papule on his right knee in January 2002. He was first presented to a surgeon for a skin biopsy. Histopathological investigation showed unspecific inflammation with some epitheloid cells present in the deeper dermis. In March 2002, the patient was first examined at the Department of Dermatology, where a second biopsy was performed. The specimen was sent to a laboratory for bacteriological examination for *M. tuberculosis* and atypical mycobacteria. The results of Ziehl-Neelsen staining, PCR for *M. tuberculosis*, and cultivation of *M. tuberculosis* and atypical mycobacteria were negative. The patient denied any contact with aquarium water, fish, or obvious trauma at the site of infection. He was a competitive swimmer and usually went to a school swimming pool once or twice a week. However, because of negative laboratory results and unspecific histology, infection with atypical mycobacteria was not considered very likely. He received topical antibiotic therapy only. In the next months, the papule on his right knee progressed to a 4 × 3 cm plaque with a purulent discharge (Figure 1). In March 2003, skin biopsy was performed again for histological examination only; it revealed chronic granulomatous inflammation with epitheloid cells and some giant cells. Differential diagnosis included lymphocytoma, chronic pyoderma, atypical granuloma annulare, sarcoidosis, and foreign body granuloma. The results of the standard laboratory examinations were within normal limits. Serological examination for *Borrelia burgdorferi* and mycological examination were negative. A pure culture of *Staphylococcus aureus* was isolated from the skin swab. In line with the results of drug susceptibility tests, the patient received systemic therapy with clindamycin for 14 days, which resulted in a slight regression of skin inflammation, but purulent discharge was still present periodically. Treatment with ampicillin for 10 days and with topical antibiotic with fusidic acid cream for several weeks followed.

The patient was lost for follow-up for a year and a half. In March 2005, he returned to our department because tender skin inflammation on his right knee persisted. He noticed exacerbation of inflammation and purulent discharge after physical activity. Therefore, the fourth biopsy was performed and the specimen was sent to a specialized laboratory for mycobacterial infections. The laboratory was informed about the suspected *M. marinum* infection and the specimen was cultivated at both 36 and 30 °C. *M. marinum* was isolated and identified with a GenoType *Mycobacterium* culture identification kit (Hain Lifescience, Nehren, Germany). The isolate was sensitive to several antibiotics (rifampicin, ethambutol, ciprofloxacin, clarithromycin, and trimethoprim-sulfamethoxazole) but resistant to isoniazid.

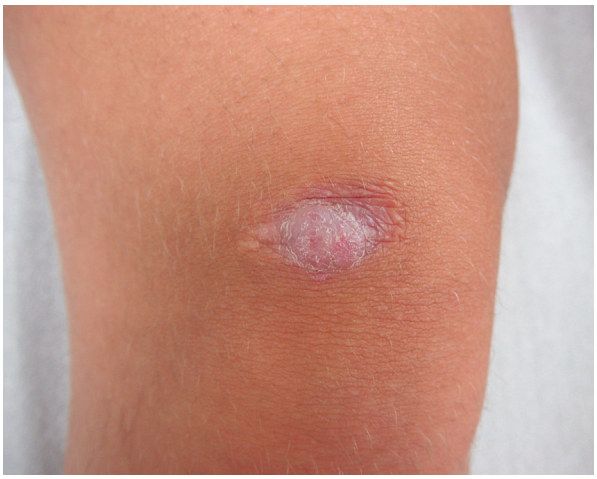

Figure 1. Erythematous plaque on the knee due to *M. marinum* infection.

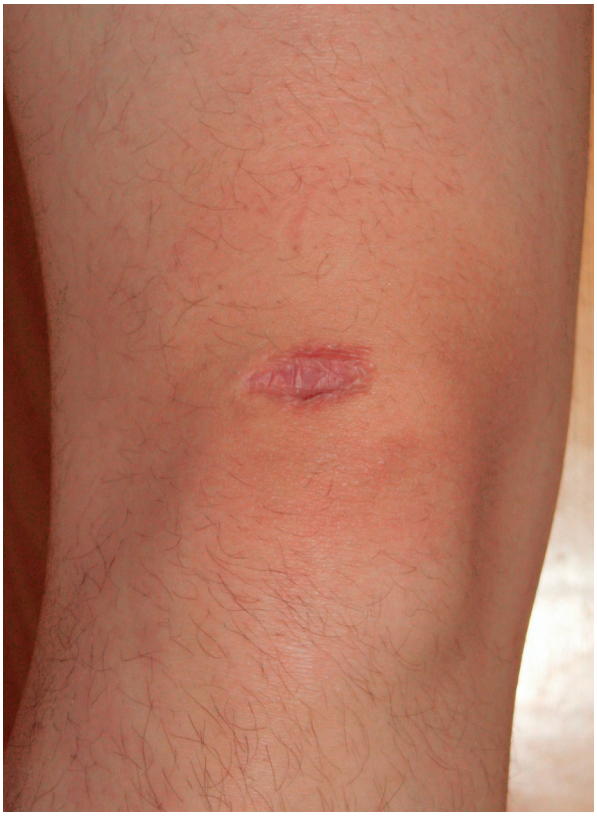

Figure 2. Residual atrophic scar 3 years after antibiotic treatment.

Treatment with trimethoprim-sulfamethoxazole (160/800 mg bid) and topical treatment with fusidic acid cream followed for 2 months. Nearly complete regression of the skin infiltrate was noticed after 1 month. Three years after the treatment, the patient is without any signs of infection and has a residual atrophic scar (Figure 2).

Discussion

Delay in diagnosis is considered more a rule than an exception in *M. marinum* infection (4). This infection is rarely seen in everyday dermatological practice; therefore awareness of this infection is low (4). The data on average time from clinical presentation to correct diagnosis vary from 1 to 27 months with a mean interval of 7 months (2). An extremely prolonged course of disseminated *M. marinum* infection, lasting 45 years, has also been reported (5).

In the case presented here, the delay in diagnosis was a consequence of various circumstances: unspecific histology at the first biopsy, inappropriate cultivation of skin specimen for atypical mycobacteria after the second biopsy, insufficient correlation of anamnestic and clinical data with laboratory and histological results, temporary loss to follow-up of the patient, and low awareness of mycobacterial skin infection among the clinicians.

The diagnosis of *M. marinum* infection should be confirmed by histology and bacteriology (2), but these goals are sometimes difficult to achieve. Therefore, the diagnosis in practice is mostly based on anamnestic data, clinical and histological features, and response to therapy (6).

Histology is often unspecific during the first 3 months of infection (1, 2, 7). The absence of epithelioid and multinuclear cells is not unusual in acute lesions (8). In our patient, the first histological examination was unspecific, probably because the biopsy was performed only 1 month after the first clinical sign. Ziehl-Neelsen staining of the skin tissue specimens was found to be positive in 9 to 13% of localized cases only, but microscopy can reveal acid-fast mycobacteria more often in disseminated disease (1, 8).

The gold standard for diagnosis of mycobacterial infection is a culture from the tissue biopsy (4). Cultures have been reported as positive in 70 to 80% of cases (1, 6). Cultivation of mycobacteria from secretions is less successful than cultivation from the tissue specimens (9). At least a 4 mm punch skin biopsy of the granuloma or even multiple biopsy specimens is recommended (6, 10).

The optimal growth temperature for *M. marinum* is 30 to 32 °C. Therefore, if mycobacterial infection is suspected, the laboratory should be alerted to this (in writing or verbally) so that they cultivate the specimen at the appropriate temperature and employ the appropriate techniques (1). Rapid transport and processing of the specimens are also important (6). The culture should be observed for 6 to 12 weeks. In the case presented here, cooperation with the laboratory was established only later.

Molecular detection of mycobacterial DNA in skin specimens or histological material has been described as a very promising method in recent years (11) but it can generate false positive results (12). There is no standardized commercially available diagnostic test on the market at the moment. Cultivation of mycobacteria on growth media is also the only method that enables drug susceptibility testing.

M. marinum infections arise after skin trauma and after contact with contaminated water. Today, the infection is often aquarium-related; in 50 to 84% of cases the affected are aquarium owners (1). Trauma after handling infected fish or shellfish can also provoke infection (1). However, in many cases the source of infection remains unknown (3); in 72% of reported cases the source of infection was not documented (3). In the recent literature, other sources or reservoirs of infections have been proposed, such as plants (4), foreign bodies from wood splinters, (9) and contaminated surgical instruments (13).

Localization of infection correlates with a traumatic etiology. Infection is usually limited to the peripheral, cooler parts of the body. In most of the reported cases in the past decades, the upper limbs were affected, especially the fingers (2, 9, 14). Among aquarium owners, the hands are most commonly affected (10). The lower extremities are rarely involved, but generally these are the knee and shin (2, 6). In the past, skin infections associated with swimming pools were frequently localized on the elbows (5, 9).

Infections related to swimming pools were very common before 1962. Due to improvement in disinfection and chlorination of swimming pool water, this source of infection is relatively uncommon nowadays and is believed to contribute to only 2.6–4.4% of all infections (1, 3, 6). Few reports of swimming pool–associated infections were published after 1962 (3, 14, 15). The concentration of free chlorine in swimming pool water should be kept between 0.4 and 1.0 mg/l to prevent infection. According to anamnestic data from our patient, the infection was most probably acquired in the swimming pool after an unnoticed trauma.

Retrospective assessment reveals that the clinical manifestation of the infection in our patient was consistent with a swimming pool granuloma. However, because infections related to swimming pools have become rare, they are usually not suspected; other diseases with similar clinical and histology findings

are considered to be more probable, especially foreign body granuloma, chronic pyogenic infection, deep fungal infections, and sporotrichosis. Single lesions are most common in immunocompetent patients, presenting papulo-nodular, verrucous, or ulcerated granulomatous inflammation with minimal purulent secretions (9). Sporotrichoid dissemination is possible in 20 to 40% of infections (1); several cases have been reported in recent years (3, 6, 9, 10, 16). In chronic infections, tenosynovitis, bursitis, arthritis, and osteomyelitis can sometimes occur (9). In immunocompromised patients, the infections are often disseminated (8, 17) and may have a more aggressive course in the transplant recipients (18). The first reports of disseminated skin infections in patients receiving etanercept (19) and infliximab therapy were published recently (15, 20, 21).

There are no standard treatment recommendations for infections caused by environmental mycobacteria because of the lack of randomized controlled trials comparing various drugs (13, 14, 22). Treatment of *M. marinum* infection should be adapted to each patient individually, according to immunological status, clinical presentation, duration, and depth of the infection (2). In the case of a localized infection, prolonged treatment with various antibiotics (e.g. clarithromycin, minocycline, doxycycline, ciprofloxacin, and trimethoprim-sulfamethoxazole) as monotherapy is recommended. Clarithromycin is favored as a first-line monotherapy according to drug susceptibility testing and due to fewer side effects (1, 2). Several reports favor this drug as the optimal agent in mono- and combination therapy (14, 23). Treatment with minocycline has also been reported as very effective (24). Monotherapy should be avoided in cases of extensive infection (8). In the sporotrichoid distribution pattern, the recommended combinations are rifampicin and ethambutol (25) or clarithromycin and either rifampicin or ethambutol (23). The recommended duration of the therapy varies considerably, depending on the severity of skin infection, and should continue for 2 to 3 weeks after all the lesions have healed (9). Some recommend at least a 3-month treatment regimen (2, 23). Cryotherapy, excision, and curettage are also possible therapeutic options in localized infections (8). Solitary cutaneous lesions in immunocompetent patients may resolve spontaneously in several months to 3 years (1). In the case presented, the patient was treated with trimethoprim-sulfamethoxazole. This drug has few side effects and was reported as extremely effective several years ago (26). The treatment lasted for only 2 months, because almost complete regression was achieved after just the 1st month of therapy. The short duration of treatment was successful because the patient was young and immunocompetent with only a solitary skin lesion.

Conclusion

To improve awareness and knowledge of *M. marinum* infection we should be reminded of this rare pathogen. In the case presented, the reasons for delayed diagnosis were discussed in order to improve the diagnosis of these sporadic infections and to stress the importance of introducing the appropriate treatment early, which is especially important in immunocompromised patients. The purpose of this work was also to remind readers that *M. marinum* infection arises most often from aquarium water, but it can still be acquired in swimming pools. However, according to recent literature, other sources of infection have also been recognized.

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AUTHORS' ADDRESSES

Mateja Dolenc-Voljč, MD, PhD, University Medical Center, Ljubljana, Department of Dermatology, Zaloška 2, 1000 Ljubljana, Slovenia, corresponding author, E-mail: mateja.dolenc-voljc@mf.uni-lj.si

Manca Žolnir-Dovč, PhD, Specialist in Medical Microbiology, Head of Laboratory for Mycobacteria, University Clinic of Respiratory and Allergic Diseases, Golnik, Golnik 36, 4204 Golnik, Slovenia