ABSTRACT

A 70-year-old, immunocompetent male presented with mildly painful and pruritic erythematous patches and vesicles on the right dorsal aspect of the distal middle finger present for four weeks. Other skin lesions or systemic symptoms were notably absent. The patient failed to respond to valacyclovir, topical triamcinolone acetonide ointment, trimethoprim-sulfamethoxazole, and cephalexin for presumptive diagnoses of recurrent herpetic whitlow, dyshidrotic eczema, and blistering distal dactylitis, respectively. Furthermore, biopsy findings were inconsistent with eczema, psoriasis, or viral or fungal infection as potential etiologies. *Mycobacterium marinum* infection was then considered due to the patient's observation that the lesion appeared three weeks after purchasing a home fish tank. *Mycobacterium marinum*, referred to as "fish tank granuloma" as a result of its typical association with aquarium exposure, is usually diagnosed clinically and treated empirically due to the organism's slow-growing nature. In light of the infection's low prevalence, large studies regarding treatment options are limited. Our patient's lesion resolved within two weeks of treatment with clarithromycin (500mg twice a day) and ethambutol (15mg/kg once a day), which was then continued for two more months. Prior to this treatment, the patient's lesion had cleared completely with minocycline; we attribute recurrence to not continuing therapy past lesion resolution.

KEYWORDS: *Mycobacterium marinum*, nontuberculous mycobacteria, aquarium, granuloma, minocycline, clarithromycin, ethambutol

CASE REPORT

Complete Resolution of *Mycobacterium marinum* Infection with Clarithromycin and Ethambutol: A Case Report and a Review of the Literature

by JOLIE KROOKS, BS; ANGELA WEATHERALL, MD; and STUART MARKOWITZ, MD

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A 70-year-old immunocompetent man presented with mildly painful and pruritic erythematous patches and vesicles on the right dorsal aspect of the distal middle finger. The patient denied paresthesia, swelling, or a reduction in sensation or range of motion. The lesion had been present for four weeks without changes in severity or morphology, though the patient noted slight improvement with valacyclovir 1g taken three times daily for three days prior to consultation.

Pertinent negatives from the patient's past medical history included no recent digital trauma, insect bites, or infections. The patient denied a dermatologic history of herpes, eczema, psoriasis, or fungal infection. Chronic medical conditions were limited to hypertension and hypercholesterolemia, while allergies were limited to rash with penicillin.

The patient is a physician and is employed as a medical school administrator, though he denied patient exposure or excessive handwashing. The patient disclosed that his wife has a history of herpes labialis. Also, he often tends to a home fish tank without using gloves. No one else tends to the fish tank. Of note, the patient noticed the skin lesion three weeks after purchasing the fish; two of the fish also died within three weeks after purchase. Social history was otherwise nonremarkable for exposure to chemicals or corrosive agents, close contact with scabies, involvement in contact sports, smoking, alcohol or chronic drug use, or risk factors for human immunodeficiency virus (HIV) infection.

Pertinent negatives from a review of systems included the absence of other skin, nail, or mucosal lesions or systemic manifestations.

On exam, the patient presented with violaceous patches and vesicles with slight honey-colored crusts just proximal to the nail bed on the right dorsal middle finger (Figure 1). Lesions were limited to the right distal middle finger and were not accompanied by swelling, warmth, or nail or lymph node involvement. There was no reduction in sensation or range of motion and there was no tenderness upon palpation. Physical examination was otherwise nonremarkable.

Considering the patient's history and presentation, herpetic whitlow and dyshidrotic eczema were the main diagnoses considered, for which the patient was respectively prescribed valacyclovir oral 1g twice daily for one week and triamcinolone acetonide 0.1% topical ointment to be applied to the affected area twice daily for two weeks. Application of emollients was also advised.

The patient presented one month later without improvement in symptoms. In the

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interim, he was prescribed trimethoprim-sulfamethoxazole and cephalexin by another physician, which also did prompt improvement. Differential diagnoses now included: recurrent hepatic whitlow, dyshidrotic eczema, acrodermatitis continua of Hallopeau, bullous tinea, and mycobacterial infection.

Shave biopsy was performed and valacyclovir was continued to cover for recurrent herpetic whitlow pending biopsy results.

On 10-day follow-up, the patient had failed to respond to valacyclovir again. Biopsy revealed a papillary dermal lymphohistiocytic infiltrate with few neutrophils, severe edema, and a fibrinohemorrhagic exudate suggestive of infectious dactylitis. Findings potentially indicative of eczema, psoriasis, or viral etiology were not observed, and Periodic acid–Schif stain failed to identify pathogenic fungal microorganisms. Nevertheless, the patient's presentation with the absence of swelling and/or warmth and his failure to respond to trimethoprim-sulfamethoxazole, cephalexin, and valacyclovir were inconsistent with a bacterial infectious dactylitis or herpetic whitlow as the leading diagnoses. The patient's failure to respond to a topical steroid also was inconsistent with dyshidrotic eczema. In considering the patient's fish tank exposure, minocycline oral 100mg twice daily was prescribed and Acid-fast Bacilli (AFB) testing of the previous biopsy sample with hematoxylin and eosin stain was requested for presumed infection with *Mycobacterium marinum*. The patient denied a biopsy for deep tissue culture. Results of AFB testing were later found to be negative.

The patient's lesions resolved completely after 12 weeks of minocycline (Figure 2).

Excluding mild photosensitivity and thrush that resolved with two weeks of fluconazole, the patient did not experience significant side effects. Nevertheless, the lesions recurred within a month of minocycline discontinuation on the original distal right middle finger and on the right fourth finger. Clarithromycin (500mg twice a day) and ethambutol (15mg/kg once a day) were prescribed, and the lesions were biopsied for deep tissue culture and polymerase chain reaction (PCR), which were both later found to be negative. The patient's lesion cleared within two weeks, and treatment with clarithromycin and ethambutol was continued for an additional two months.

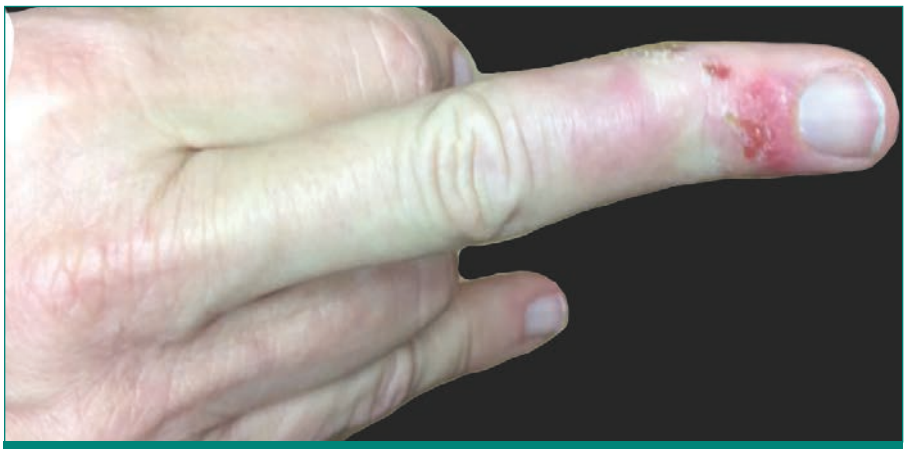

FIGURE 1. Violaceous patches and vesicles limited to the right dorsal distal middle finger

DISCUSSION

The incidence of cutaneous nontuberculous mycobacterial (NTM) infections, at 1.3 per 100,000 person-years, has increased by nearly three-fold from 1980 to 2009 as reported by a Minnesota population-based study. Of the NTM infections, *Mycobacterium marinum* infection was reported as the most common (45% of cases).[1]

Mycobacterium marinum is commonly referred to as "fish tank granuloma," as infection is attributed to aquarium exposure in the majority of cases (84%).[2] Other less commonly implicated sources of infection include fish and shellfish, as well as salt, brackish, or fresh water. Swimming pool-related exposure is scarce and has been further minimized by current disinfection and chlorination procedures.[3] Most reported cases have incubation periods of less than four weeks.[3]

Consistent with the short incubation period of the cases reported in the literature, our patient's lesion developed within three weeks after purchasing the fish tank. Different strains of *Mycobacterium marinum* vary in their effects on fish and humans. In a study of zebra fish, Van der sar reported that the strain transmittable to humans was lethal to fish within three weeks, whereas the strain with limited transmissibility to humans produced a disease in fish with a more indolent course.[4] Analogously, our patient noted that his skin lesion developed concurrently with the deaths of two of his fish.

Lesions most commonly present on the upper extremity (95%), particularly the hand (80% of upper extremity lesions), and may involve more than one location (67%).[2] There are no pathognomonic cutaneous presentations.

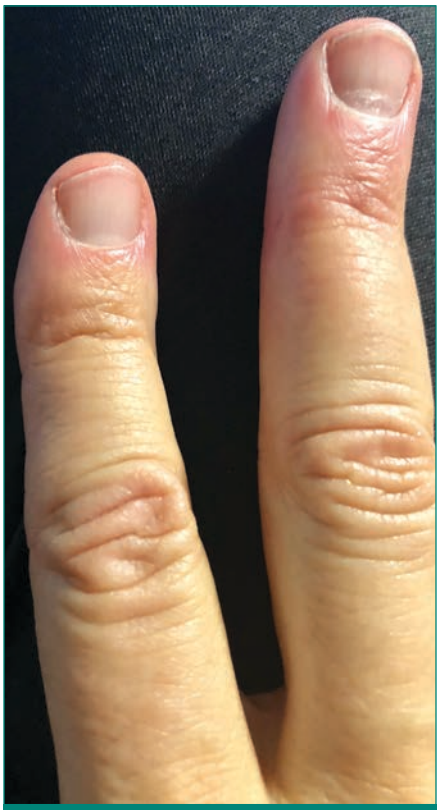

FIGURE 2. Complete resolution of lesions in response to 12 weeks of oral minocycline (100mg twice daily)

Presentation may range from painful or painless, single or multiple erythematous papules, nodules, plaques, or verrucous lesions with or without crust and/or ulceration. Lesions have commonly been reported to follow a sporotrichoid spread without accompanying lymphadenopathy. Categorization of the lesions into three types may guide treatment: Type 1 lesions are self-limited, 1cm to 2cm superficial erythematous papular or verrucous lesions that

may be treated with antibiotics if remission is not observed; Type 2 lesions are subcutaneous granulomas that should be treated with antibiotics; and Type 3 lesions denote the involvement of deeper structures (e.g., tendons, joints, bones) that require combined antibiotic therapy with surgical debridement.[5–8] Though disseminated disease is rare, deep tissue involvement, which might result in tenosynovitis (24%), arthritis (11%), and osteitis (5%), is a significant prognostic indicator of treatment response; thus, high clinical suspicion is essential to prevent disease progression.[2]

The diversity of potential lesions leads to a diverse differential diagnosis, including sporotrichosis, leishmaniasis, cutaneous tuberculosis, tuberculoid leprosy, verruca vulgaris, sarcoidosis, psoriasis, and foreign body reaction. Accordingly, in addition to a history consistent with aquatic exposure, biopsy with culture is essential for definitive diagnosis; though, due to the organism's slow-growing nature, diagnosis is often made clinically and presumed *Mycobacterium marinum* infection is treated empirically.

Biopsy must be taken from a nonulcerated area in close proximity to the lesion. *Mycobacterium marinum* is a catalase-positive, slow-growing aerobic organism that grows optimally on Lowenstein-Jensen medium at 30°C to 32°C within 2 to 5 weeks and turns yellow with exposure to light. Pathologic findings are variable and nonspecific, depending on the age of the lesion. Acute lesions present with a mixed inflammatory infiltrate that progresses (six months) to a noncaseating granuloma with fibrinoid necrosis.[9] Sensitivity of AFB smear is low; 95% of cultures are AFB smear-negative.[10] Utilization of PCR as a faster, more sensitive diagnostic tool is becoming increasingly recognized.[11,12] Our patient's AFB smear and PCR results were both negative. While PCR has an improved sensitivity relative to that of AFB smear, sensitivity is still notably low (51%).[13] Our patient's negative culture also was not indicative of an alternative diagnosis, as only 70 to 80 percent of cultures are positive, likely due to the stringent temperature requirements for optimal growth.[14] Accordingly, the most critical components to diagnosis used in practice include patient presentation and accompanying risk factors and response to treatment.

Large studies of efficacious treatment options are limited due to infection rarity. Complete remission is common (87%); poor response to treatment is associated with specific lesion characteristics (i.e., the presence of deep tissue involvement or ulceration) rather than the specific antibiotic regimen.[2] Clarithromycin (500mg twice a day), minocycline (100mg twice a day), doxycycline (100mg twice a day), and trimethoprim-sulfamethoxazole (160/800mg twice a day) can be used as monotherapy for superficial infection; however, the combination therapy of rifampicin (600mg once a day) and ethambutol (15mg/kg once a day) might be necessary for resistant or more severe presentations. Ciprofloxacin or a combination of isoniazid, streptomycin, and pyrazinamide is not recommended. Susceptibility testing is reserved for cases of treatment failure and culture positivity following three months of therapy. Duration of antibiotic therapy may range from one to 25 months (median duration: 3.5 months) and it is recommended to continue therapy with two active antibiotics for 1 to 2 months following lesion resolution. Surgical debridement is typically only recommended in patients who are refractory to antibiotic therapy or who present with deep tissue involvement. Spontaneous remission has been reported in untreated, immunocompetent hosts.[2,10,11,15] Though not used in our patient, thermotherapy, in isolation or in combination with standard antibiotics, has also been reported as an effective therapy, even in treatment-refractory cases. Thermotherapy is particulary relevant to treating *Mycobacterium marinum* infections considering the bacteria's optimal growth temperature (30°C to 32°C). Nevertheless, it is typically recommended that thermotherapy be utilized in conjunction with antibiotics in order to prevent relapse and/or dissemination.[16–19]

Our patient's lesions resolved completely after 12 weeks of minocycline oral 100mg twice daily, consistent with the typical treatment duration reported in the literature. Retrospective studies have also reported frequent response to minocycline: 10 of 14 (71%)[6]; 22 of 24 (92%)[2]; 3 of 3 (100%)[20]; 5 of 5 (100%)[21]; 11 of 11 (100%)[22]; and 12 of 12 (100%)[23] cases, respectively, resolved.

Clarithromycin has also been reported as an effective therapy in case reports and retrospective studies. For instance, Bonnet et al[24] described the success of clarithromycin monotherapy (2g once daily for 50 days) in treating an HIV-positive patient with culture-positive *Mycobacterium marinum* infection refractory to both a five-month regimen of ofloxacin and minocycline and a combination of intravenous rifampin, ciprofloxacin, and amikacin. Antiemetics were also prescribed with clarithromycin due to gastrointestinal upset. No recurrence was noted at the six-month follow-up. The authors also reported on the treatment of an immunocompetent patient with clarithromycin and ethambutol, prescribed together for a synergistic effect to target the patient's deeper lesions (i.e., multiple subcutaneous nodules). Therapy was well tolerated and the lesions cleared within 10 to 15 days, with no recurrence on two-year follow-up.[24] Clarithromycin efficacy, as both monotherapy or in combination with other antimicrobials, has been documented in other case reports as well, including in patients with deeper infections and/or those refractory to multiple other therapies (e.g., trimethoprim-sulfamethoxazole, ciprofloxacin, and ethambutol). Even with doses smaller than that administered by Bonnet et al (500mg once or twice daily vs. 2g once daily), tolerability ranged from well tolerated to needing to stop treatment due to nausea.[25–27] In a larger study, Feng et al[28] reported that, of 18 patients with PCR-confirmed *Mycobacterium marinum* infection treated with clarithromycin monotherapy (500mg twice daily) or clarithromycin (500mg twice daily) in combination with rifampicin (600mg once daily) and ethambutol (1g once daily), 15 (83%) achieved complete remission with no recurrence on six-month follow-up. There was no significant difference ($P>0.05$) in cure rate between treatment with monotherapy and combination therapy. Time to achieve complete remission averaged three months (11.6 weeks monotherapy, 12.7 weeks combination), and therapy was continued for one month following complete remission. Aubry et al[2] reported a similar cure rate in patients with skin-limited infection treated with clarithromycin-containing regimens (18 of 20 patients, 90%).

While clarithromycin is a suitable alternative to minocycline, minocycline has been reported as the most frequently prescribed therapy, providing favorable results with minimal side effects, and was therefore the first antimicrobial prescribed for our patient.[23] Recurrence of our patient's lesions may be due to minocycline resistance; however, this also reflects the

importance of continuing therapy with two active antibiotics following resolution.

While trimethoprim-sulfamethoxazole has also been reported as a successful treatment option for superficial infection, the duration of the patient's treatment (10 days due to suspicion for infectious dactylitis) was not long enough to assess treatment efficacy. Given the typical range of therapy (between 1 and 25 months), medication should be administered for at least a month before considering an ineffective response.

CONCLUSION

In summary, we report on a case of a superficial *Mycobacterium marinum* infection of the right distal middle finger of a 70-year-old, immunocompetent male with a history significant for aquarium exposure. Accordingly, this case illustrates the importance of considering this infection in the differential diagnosis of persisting upper extremity lesions in both immunocompetent and immunocomprised patients with a history of aquarium exposure. The patient experienced complete resolution of the lesions after 12 weeks of minocycline, but recurrence illustrates the necessity of continuing treatment following lesion resolution.

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