

Tenosynovitis and Sporotrichoid Disease Due to *M. marinum* on a Patient under Anti-TNF α Therapy^{*#}

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Received September 26th, 2013; revised October 26th, 2013; accepted November 4th, 2013

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ABSTRACT

There have been several reports of tuberculosis (TB) and, less frequently, of nontuberculous mycobacterial (NTM) infections in association with tumor necrosis factor α inhibitor (anti-TNF α) therapy. *Mycobacterium marinum* is a NTM with a distinct epidemiology and is infrequently responsible for disease in humans. Most commonly, it causes localized skin infections, but in 20% to 40% of cases, it involves deeper structures. Disseminated disease is exceptional and has been reported to occur only in immunocompromised patients. The authors report a clinical case of tenosynovitis and sporotrichoid disease due to *M. marinum* in a 45-year-old male patient under anti-TNF α therapies for spondyloarthritis. Along antimicrobial therapy, the patient underwent surgical debridement and after two years he is still on treatment but substantially improved. A few cases of *M. marinum* infection occurring in patients treated with anti-TNF α drugs have been reported. The diagnosis of infection due to *M. marinum* requires a high index of suspicion from a properly obtained exposure history and is important so that efficient diagnostic approach and treatment are ensured.

Keywords: *Mycobacterium marinum*; Anti-TNF α Drugs

1. Introduction

Human infection due to *Mycobacterium marinum* was reported as a tuberculoid infection and historically recognized in people using public swimming pool. Most infections occur after contact with contaminated water from “swimming pool” or “fish tank”, most frequently after minor abrasion, laceration, puncture or bite wounds. Human infections with *M. marinum* are localized primarily to the skin; most commonly, *M. marinum* presents as a solitary papulonodular lesion on a finger or hand, and in some cases, it takes on a “sporotrichoid” form with one or more nodules in the proximal skin along paths of presumed lymphatic spread. Deep infections such as tenosynovitis (the most frequent), osteomyelitis, arthritis and bursitis occur in 20% to 40% of cases. A few cases of *M. marinum* in patients treated with anti-TNF α therapy have

been reported.

2. Clinical Case

On December 2008, a 45-year-old white man, with a previous history of spondyloarthritis, with long lasting complaints of articular inflammatory pain on the elbows, shoulders, hip and knees treated with non-steroidal anti-inflammatory drugs (NSAIDs), developed two papulonodular erythematous lesions on the second and the third finger of the right hand (**Figure 1**). He was responsible for the maintenance of his domestic fish tank.

Although he had no recollection of trauma, he exhibited a puncture-like wound on his right thumb. He was medicated with flucloxacillin. On the following six months, the papulonodular lesions remained the same but since he reported worsening of articular complaints on the right hand, local injection with corticosteroid was done, without improvement. Later, he had worsening of his spondyloarthritis refractory to conventional therapy, so he was started on etanercept after two months of isoniazid due to positivity of both purified protein derivative (PPD) tuberculin skin testing and gamma inter-

*Statements: All persons gave their informed consent and authorized publication of this case report. All authors declare that the submitted work has not been published before (neither in English nor in any other language) and that the work is not under consideration for publication elsewhere.

#Conflict of interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Figure 1. Initial papulonodular lesion.

feron release assay (IGRA). About ten months later, there was intensification of the swelling and redness of the second and the third finger of the right hand, along with worsening pain and functional limitation. Etanercept was stopped and he was started on adalimumab. The hand lesions evolved to tenosynovitis and the patient underwent synovectomy of the hand and fingers on November 2010, six weeks after adalimumab was stopped (**Figure 2**). Acid-fast bacilli were seen in the histological tissue surgically removed and *M. marinum* grew in the culture of tissue. The susceptibility testing showed *M. marinum* sensible to rifampin, ethambutol, clarithromycin and amikacin.

About eleven months later treatment with rifampin, ethambutol and clarithromycin was started, he developed multiple cutaneous nodular lesions of the right arm, some with pus-draining fistulae (**Figure 3**). He underwent a second surgery, with division of the muscle, tendon and hand fascia. After 2 years, the patient is still on treatment (with minocycline) but he has significantly improved.

3. Discussion

The incidence of nontuberculous mycobacteria (NTM) associated disease has increased markedly in the last decades, mostly due to the advent of the AIDS epidemic and the introduction of immunosuppressive therapies [1]. Infection or reactivation of *M. tuberculosis* and atypical mycobacteria has been documented as a risk of tumor necrosis factor α inhibitor (anti-TNF α) therapy [2,3].

Almost all NTM can cause cutaneous disease, the most common species in the USA and Europe being *M. marinum* and *M. ulcerans*, and the rapidly growing mycobacteria (RGM) *M. abscessus*, *M. fortuitum* and *M. chelonae* [1,4-7]. Immunosuppression seems to be an important risk factor in the development of lesions due to these agents, with the possibility of deep tissue invasion, even in the absence of previous skin trauma [1]. In the case described, even though the patient presented what could be interpreted as a puncture-like wound, he had no memory of preceding skin injury of the hand.

M. marinum was first isolated in 1951 from a patient

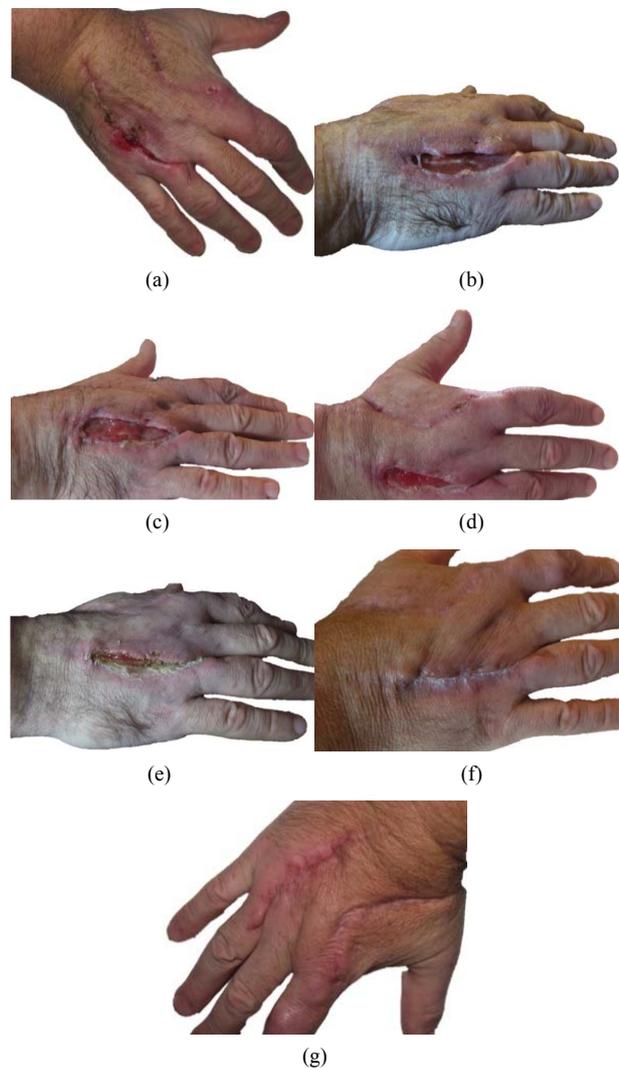


Figure 2. (a)-(g) progression after synovectomy, with deep tissue exposure.

with a “swimming pool granuloma” and since then, *M. marinum* infections have occurred after contact with contaminated water from swimming pools and home aquariums [8]. However, *M. marinum* infections are rare and their incidence was recently estimated to be less than 1 case per 100,000 inhabitants per year [9].

Similarly to the lesion developed initially by our patient, *M. marinum* infection is usually a cutaneous disease characterized by a solitary papulonodular lesion on a finger or hand or a suppurating abscess at the site of trauma, but patients often do not seek medical attention until symptoms become more florid [10]. Frequently, the clinical course is indolent, with delayed presentation and diagnosis occurring after several months. In some studies, the mean delay in presentation was 4.9 (0.3 - 120) months [10] and 7.7 (range, 1 - 36) months [11].

In the present case, the diagnosis of *M. marinum* associated disease was delayed, mostly due to the tenosyno-

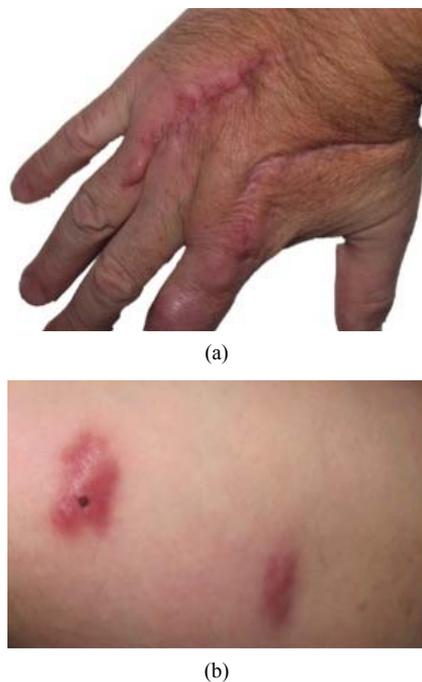


Figure 3. (a) and (b): Sporotrichoid nodular skin lesions on the right hand and arm.

vitis being attributed to the patient's underlying disease. Even though clinically suggestive, the initial papulonodular lesions were not integrated in the patient's exposure history, especially the frequent fish tank manipulation. Lesions are usually singular, but there can occur multiple ascending lesions along paths of presumed lymphatic spread resembling the infection by *Sporothrix schenckii* ("sporotrichoid disease"), as it occurred in our patient after incomplete drainage. Deep infections such as tenosynovitis (the most frequent), osteomyelitis, arthritis and bursitis occur in 20% to 40% of cases and disseminated disease is only reported in immunocompromised patients [12].

Despite the scarce number of cases that are published in the English literature (less than 10 to our knowledge), the uncommon presentation of our case exhibits similarities with the described, most frequently reports of *M. marinum* infection in patients with rheumatoid arthritis or inflammatory bowel disease treated with infliximab or etanercept, along with systemic corticosteroids.

The diagnosis of *M. marinum* infection can be challenging. Apart from being a rare agent of cutaneous infection, only in less than half of the reported cases did the skin biopsy or wound fluids yield a positive smear (31%) or a positive culture (40%) [10,13-16]. Additionally, misdiagnosis is frequent and in most cases that are described, the diagnosis usually requires biopsy or surgery [10].

PPD tuberculin skin testing is positive in most cases [17] because of cross-reaction with *M. tuberculosis*. In

the present case, the positivity of both PPD tuberculin skin test and IGRA assay were most likely due to the *M. marinum* infection yet to be diagnosed, erroneously interpreted as latent *M. tuberculosis* infection.

In all cases that are published in the literature, the microbiologic and cultural tests remain persistently negative, even if worsening of the lesions or new ones occur, after antibiotic treatment is started.

No controlled studies have been conducted to evaluate optimal treatment regimens for *M. marinum* infection. Patients with uncomplicated, localized skin infections can usually be treated successfully with antibiotic monotherapy. Combinations of two or more antibiotics are used for more serious infections and typically contain combinations of clarithromycin and minocycline-doxycycline or rifampin-ethambutol and co-trimoxazole for a minimum of 3 to 6 months. Antibiotic resistance in *M. marinum* is relatively rare in strains isolated from nature, but most isolates are intrinsically resistant to isoniazid and pyrazinamide and produce β -lactamase. Resistance to doxycycline and rifampin has been described [12].

The clinical response is generally slow regardless of the drug(s) utilized, so extended periods of treatment are required. The treatment duration referred in some of the studies published is very long: 3 to 6 months of therapy for localized disease and ≥ 12 months for disseminated disease [12], a mean duration of 7.2 (range, 0 - 29) months [10]; in one study, the treatment duration ranged from 4 to 38 (mean, 14.9) weeks [13]; and in a French study, the treatment duration ranged from 1 to 25 (median, 3.5) months [9].

Apart from its almost always important contribute to diagnosis, surgery is frequently necessary to successful treatment of deep infections in immunosuppressed patients [18]. Some authors also describe the more prolonged persistence of skin lesions in immunocompromised patients than in normal hosts, with surgical treatment often being required in the former group [1].

The initial misdiagnosis of the *M. marinum* osteoarticular infection can lead to intralesional injection of corticosteroid that favors local dissemination. In some studies, steroids injections into the lesion, persistent drainage sinus tract after several months of antimicrobial therapy, and persistent pain were associated with an unfavorable clinical course and delayed healing of the wound, which necessitated surgical debridement [19].

The extension of the cutaneous infection to deeper structures in this case was probably related to the initial intensification with immunomodulating biologic therapy, as well as the initial non-aggressive surgical approach, which probably didn't eliminate the infectious suppurative foci, essential to a favorable response to medical treatment. Despite the severity of the clinical presentation in our case, similarly to the cases published, an in-

tensive surgical approach along with extended antibiotic treatment led to an excellent functional outcome [9,10,13].

However, the optimal treatment of the persistent rheumatologic disease in these patients is yet to be defined. While the discontinuance of the immunomodulating biologic agents is essential to achievement of cure and full recovery, some authors report safe re-exposition to anti-TNF α therapy after successful bacterial elimination [20].

4. Conclusion

The deep muscular and articular involvement by *M. marinum* related to immunomodulating biologic therapy described in this case is rarely reported. Since the patients who require anti-TNF α therapies are usually at higher risk of developing infections given their underlying disease and prior or concurrent treatment with other immunosuppressive drugs, a high index of suspicion for the infectious complication is needed. A proper exposure history, particularly in less common clinical presentations, is very important. The diagnosis of *M. marinum* infection is difficult, because the presentation is often insidious and non-specific, especially when water or fish exposure is not established. The diagnosis relied on isolation of acid-fast bacilli subsequently identified as *M. marinum*. In this case, *M. marinum* infection presented as two papulonodular lesions on a hand and progressed to severe tenosynovitis after anti-TNF α therapy and took a "sporotrichoidform" after incomplete drainage. The treatment required aggressive surgery, along with extended anti-infectious therapy and discontinuance of the immunomodulating drugs.

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