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***Mycobacterium marinum* infection contracted from seaweed wrap in a psoriasis patient undergoing treatment with adalimumab.**

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Abstract

We report a patient with psoriasis who developed *Mycobacterium marinum* (*M. marinum*) infection after seven years of treatment with adalimumab, a human anti-TNF (tumor necrosis factor) monoclonal antibody. TNF is a pro-inflammatory cytokine that plays a central role in the pathogenesis of psoriasis and a number of other immune-mediated inflammatory diseases. TNF plays an important role in granuloma formation and host defense against mycobacterial infections. Several cases of atypical mycobacterial infections in patients on TNF inhibitors have been reported. To our knowledge, this is the second reported case of *M. marinum* infection in a patient on adalimumab for the treatment of psoriasis.

Keywords: psoriasis, TNF, adalimumab, *Mycobacterium marinum*

Introduction

TNF is a pro-inflammatory cytokine that plays a central role in the pathogenesis of psoriasis and a number of other immune-mediated inflammatory diseases. TNF plays an important role in granuloma formation and host defense against mycobacterial infections [1]. Several cases of atypical mycobacterial infections in patients on TNF inhibitors have been reported [2]. To our knowledge, this is the second reported case of *M. marinum* infection in a patient on adalimumab for the treatment of psoriasis [3]. We

identified two other cases of *M. Marinum* infection in patients on adalimumab for the treatment of psoriatic arthritis [4]. In our patient's case, infection was obtained through exposure to seawater.

Case Synopsis

A 53-year-old man presented with a 3-week history of a red, hot and swollen left thumb. He worked at sea, servicing lighthouses and navigation aids. Eight weeks earlier, while sawing timber on the deck of a ship, he sustained an abrasion proximal to the nail fold on the dorsum of the left thumb. Two days prior to presentation he lacerated his thumb while cutting cable from a buoy, reopening the original wound. He wrapped his thumb in seaweed to stop the bleeding.

He was diagnosed with psoriasis at the age of sixteen and with psoriatic arthritis aged nineteen. Previous treatments included PUVA, fumaric acid esters, and etanercept. He was commenced on adalimumab aged forty-three, and his psoriasis was well controlled on 40mg subcutaneously every other week with a psoriasis area and severity index of 3.4.

Prior to presentation, he had been treated by his general practitioner with two courses of oral flucloxacillin and benzylpenicillin.

He had a well demarcated erythematous plaque of the left thumb (**Figure 1**), associated with edema of the hand and sporotrichoid lymphangitis of the left forearm. He was unable to flex his thumb but remained systemically well. A clinical diagnosis of



Figure 1. Left hand at initial presentation, showing well demarcated, erythematous plaque with associated edema of the thumb.

atypical mycobacterial infection was made. The full blood count and C-reactive protein were normal. An X-ray of the left thumb showed soft tissue swelling and no evidence of osteomyelitis. Punch biopsies were sent for mycobacterial and fungal culture and histopathological examination. Adalimumab was discontinued and minocycline 200mg daily was started.

Histological examination identified a superficial and deep perivascular lymphohistiocytic infiltrate with several non-caseating granulomas present consistent with an atypical mycobacterial infection (**Figure 2**). No acid fast bacilli were seen with Ziehl-Neelsen staining and PCR for DNA from genus *Mycobacterium* was negative. Mycobacterial culture became positive for *Mycobacterium marinum* three months after initial presentation.

Edema and erythema of the left thumb reduced after four days of minocycline therapy. The infection continued to slowly improve, however, his psoriasis began to flare. Adalimumab 40mg subcutaneously

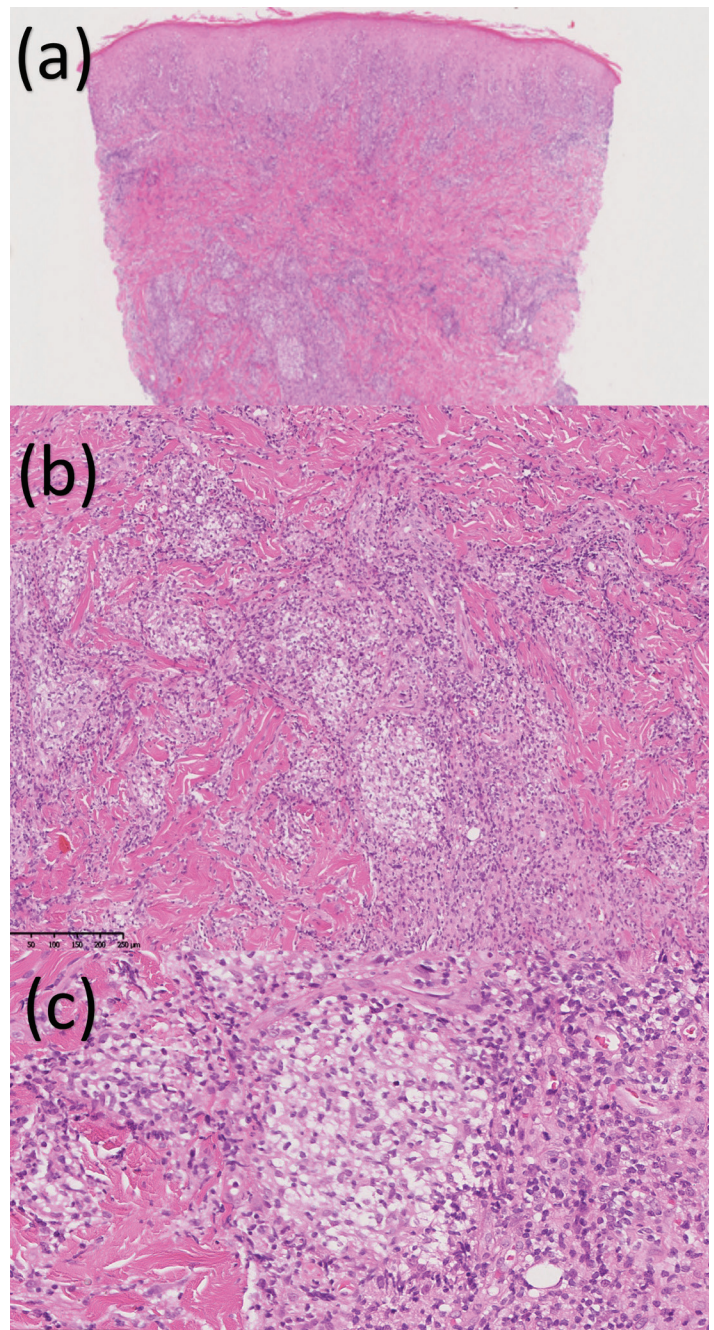


Figure 2. Punch biopsy demonstrating non-caseating granulomatous inflammation.

fortnightly was re-commenced after six months of minocycline therapy, with no recurrence of infection (**Figure 3**). Minocycline was continued in conjunction with adalimumab for a further six months without any relapse of the infection.

Case Discussion

Non-tuberculous mycobacteria (NTM) are a large, diverse group of environmental organisms with over 120 recognized species. They cause a variety of diseases in humans including pulmonary disease and skin and soft tissue infections [5]. Of 105 confirmed or



Figure 3. Significant improvement following 6 months of treatment with minocycline.

probable cases of NTM in patients who were receiving anti-TNF inhibitors reported to the US Food and Drug Administration from 1999-2006, *M. avium* was the most common etiologic organism and infliximab was the most commonly associated anti-TNF drug [2].

We identified seven reports of *M. marinum* infection in patients prescribed adalimumab. These include a 50-year-old woman treated with adalimumab for rheumatoid arthritis who presented with a lesion of the right index finger rapidly followed by the development of nodules of the forearm. She had a history of regularly cleaning a fish tank. She was treated with minocycline and clarithromycin with a good response [6].

Bakker described two other cases of *M. marinum* cutaneous infection in patients on adalimumab [4]. A 60-year-old man treated with adalimumab, methotrexate, and prednisolone for rheumatoid arthritis presented with papules and nodules of the lower back, hand, and legs. A 55-year-old man on adalimumab for psoriatic arthritis developed *M. marinum* infection of his left calf following minor trauma. Both patients had a history of freshwater fishing. They were treated with ethambutol and clarithromycin and in each case re-activation of infection ensued upon re-introduction of TNF inhibitors. Kump described a case of *M. marinum* infection in a patient on adalimumab for Crohn disease presenting with nodular skin lesions of the right foot eight weeks after acquiring a superficial skin injury in the Thai sea [7]. Kaneko recently reported a case of

M. marinum in a patient on adalimumab for psoriasis. The source of infection was not reported in this case [3]. Tomas et al. reported a case of a 49-year-old who owned a fish tank and was on adalimumab for the treatment of ankylosing spondylitis. He developed *M. marinum* infection of his right hand [8].

M. marinum is a waterborne mycobacterium that infects many fish species with worldwide distribution [5]. Infection in humans is infrequent, usually limited to the skin, often preceded by minor trauma, and related frequently to fish tank exposure [9-11]. After an incubation period of 2-6 weeks, *M. marinum* infection typically presents with plaques or nodules, most frequently of the upper limb, commonly associated with sporotrichoid spread. Definitive diagnosis is confirmed by isolation and identification of the organism and cultures should be observed for six weeks before they are declared negative [12].

There is no established treatment of choice for *M. marinum* infection. By standard susceptibility testing, *M. marinum* isolates are susceptible to rifampin, ethambutol, and minocycline. They are intermediately susceptible to streptomycin and resistant to isoniazid and pyrazinamide [13]. Isolates are also susceptible to clarithromycin, sulfonamides, and trimethoprim sulfamethoxazole. There have been no comparative trials of treatment regimens for skin and soft tissue infections caused by *M. marinum*. Optimal treatment should include two active agents for 1 to 2 months after resolution of lesions, typically 3-4 months in total [14]. The median treatment time with antibiotics in 63 reported cases of *M. marinum* was 3.5 months and 87% of patients were cured with therapy that included clarithromycin, rifampicin, or tetracyclines [10]. Treatment failure was related to deep structure involvement but not to any antibiotic regimen. Clarithromycin and ethambutol are likely to provide an optimal balance of efficacy and tolerability for most patients, with the addition of rifampin in cases of osteomyelitis or other deep structure infection [13]. Minocycline is amongst the most frequently reported effective treatments and can be used for more superficial soft-tissue infections [12]. Drug susceptibility testing is only recommended for patients who remain culture positive after several months of therapy [5].

Conclusion:

We report a patient with psoriasis who developed *Mycobacterium marinum* (*M. marinum*) infection after seven years' treatment with adalimumab, a human anti-TNF monoclonal antibody. Although *M. marinum* infection is frequently related to fish tank exposure ("fish tank granuloma") both salt water and fresh water exposure are implicated as described above. This case illustrates the risk of non-tuberculous mycobacterial infection in patients who are immunosuppressed as a consequence of treatment for psoriasis.

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