SHORT REPORT

A case of opportunistic skin infection with Mycobacterium marinum during adalimumab treatment in a patient with Crohn's disease☆

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Abstract

Opportunistic infections, especially reactivation with M. tuberculosis, are major complications during treatment with anti-TNF agents. Infections with atypical mycobacteria like Mycobacterium marinum are rare and tend to turn into a difficult and prolonged course due to delayed diagnosis. This is the first case of M. marinum infection during adalimumab therapy in a patient with Crohn's disease. The most important diagnostic step was a detailed medical history as PCR tested for M. tuberculosis and for atypical subspecies was false negative. Up to now a discontinuation of anti-TNF therapy has been recommended, however, there is no consensus about the reintroduction of biologicals after sufficient anti-infective therapy. In this patient anti-TNF therapy had to be reintroduced because of increasing activity with no relapse of M. marinum after a follow-up of 12 months.

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1. Introduction

Adalimumab is a fully human anti-TNF monoclonal antibody which has been approved in the treatment of Crohn's disease (CD). Among the major complications are opportunistic infections. In recently published literature, among others, Mycobacterium tuberculosis, Listeria spp., Histoplasma capsulatum have been observed in association with the use of anti-tumour-necrosis-factor (anti-TNF) agents.1,2 However, some rare cases of atypical mycobacterial infections have

Abbreviations: CD, Crohn's disease; anti-TNF, anti-tumour-necrosis-factor; IBD, inflammatory bowel disease; TST, Tuberculin skin test; IGRA, interferon-gamma release assay; CRP, C-reactive protein.
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been reported.3–5 One of these, *Mycobacterium marinum*, is known to cause infective skin lesions. However, the proper diagnosis of the infective agent is frequently missed, which leads to delayed treatment. In immunocompetent individuals skin infections are mainly localized lesions, better known as fish tank or swimmer’s granuloma, disseminated disease with local spread have occurred only in single cases.5–8 However, the majority of disseminated and aggressive disease are presented in immunocompromised patients, resulting in tendosynovitis, septic arthritis or osteomyelitis.9,10

We report the first case of a *M. marinum* infection developed during adalimumab therapy in a patient with CD.

2. Case description

A 40-year-old male patient presented with multiple nodular skin lesions on the right foot to our outpatient clinic for inflammatory bowel disease (IBD). He had a 20-year medical history of CD leading to previous intestinal resections. Former medical therapy including azathioprine and methotrexat had not shown sufficient clinical response. Therefore, anti-TNF therapy with adalimumab was started as a monotherapy in August 2008. The colonoscopy, which was performed previous to initiating anti-TNF treatment, revealed active disease with incipient anastomotic narrowing Rutgeerts i4. Chest X-ray as well as tuberculin skin test (TST) were inconspicuous. An interferon-gamma release assay (IGRA) (Quantiferon®) test was not performed at this stage. After two months of adalimumab monotherapy with 40 mg every 2nd week, the patient acquired a superficial skin injury of his right foot in the Thai sea in October 2008. In December 2008, 8 weeks after the injury, the patient observed first nodular skin lesions but underwent no further clinical examination. In June 2009, he presented in the course of his routine visit to our outpatient clinic with an erythematous scaly infiltrating nodule, 3×2 cm in size, on the lateral side of his right foot and multiple smaller lesions on his right wrist (Fig. 1). He was in a good general condition, presented with normal blood counts, and a slightly elevated C-reactive protein (CRP). CD was in clinical remission under the ongoing adalimumab therapy. Skin biopsy was taken and histology revealed a dense lymphohistiocytic infiltrate and granuloma with giant cells. Furthermore, Ziel Neelson staining was positive for acid fast bacilli. The tissue sample was further processed for microbiological tests. As PCR for *M. tuberculosis* as well as for atypical subspecies was negative, adalimumab therapy was continued till the result of the biopsy culture was available. Meanwhile, an empirical antibiotic therapy with ciprofloxacin and later doxycycline was started, but, despite of this therapy, the lesions had spread to the right lower leg. Four weeks after initiating antibiotic therapy, bacterial culture revealed the diagnosis of *M. marinum* infection. A repeated tuberculin skin test as well as IGRA (Quantiferon®) tested positive, whereas chest X-ray showed again no evidence of manifest, pulmonary tuberculosis. Adalimumab was discontinued and anti-infective therapy was changed to rifampicin/ethambutol. After 4 months the skin lesions had resolved apart from a light hyperpigmentation (Figs. 2 and 3). Antibiotic therapy had been prescribed for a total of 7 months, while adalimumab was stopped. In August 2010 symptoms of stenosing CD aggravated again. The colonoscopy revealed active disease with anastomotic narrowing Rutgeerts i4. Blood counts and CRP had still been unremarkable. Anti-TNF therapy was resumed with infliximab in March 2011, notably to ensure regular visits in the outpatient clinic. No prophylactic anti-infective treatment was prescribed. A follow-up after 12 months showed no reactivity of the skin lesion.

3. Discussion

*M. marinum* is a free-living mycobacterium subspecies, whose natural habitat is water. Mycobacteriosis of fish has become an increasing worldwide chronic progressive disease. Human infection may be caused by direct injury by fish fins or occur after a cutaneous trauma and exposure to contaminated water.11 Due to its low culture temperature and inhibition of growth at 37 °C, the infection is mostly limited to the skin, though it may also reach deeper structures.12 The mean incubation period is 7 months.13 The severity of the disease depends on immune status, extension of cutaneous injury, and direct inoculation.14

Disseminated infections have been reported and usually occur in immunocompromised patients. Especially patients receiving corticosteroid monotherapy or combination – therapy, as well as patients treated with anti-TNF in combination with other immune modulating substances run the risk of severe and critical illness.10,15 Our patient presented with a rather benign course of the infectious disease, despite of local spread, prolonged diagnosis and ongoing anti-TNF therapy. A few cases of *M. marinum* infection complicating anti-TNF therapy of Crohn’s disease have been reported under infliximab,3–5 but not yet under adalimumab. All of the four quoted cases had a specific history. One patient sustained a previous cutaneous trauma while cleaning a fish tank, the others had no memorable skin trauma, but were either caring for fish in a domestic aquarium, cleaned fish bowels frequently, or went swimming in a Mediterranean swimming pool. In each patient, the infection was limited to the skin although prolonged diagnosis led to a local spread in all cases. Infliximab was discontinued in all patients and tuberculostatic therapy started resulting in full recovery.

Figure 1 Skin manifestation of *Myobacteria marinum* infection. First presentation in June 2009; erythematous 3×2 cm, scaly infiltrating nodule and multiple smaller lesions on the patients right foot under ongoing adalimumab therapy.
In the adalimumab safety study, only 1.8% of a total of 3160 patients experienced opportunistic infections, however, not one single atypical mycobacterium was described. Among patients treated with the biologics etanercept and infliximab for rheumatoid arthritis, the rate of cutaneous infections such as erysipelas, furuncle, or herpes was even 7.2%.

Diagnosis of *M. marinum* infection is difficult and prolonged as the PCR of the biopsy is often false negative. The long-acting bacterial culture is the most reliable diagnostic procedure, however, some false negative cases may still occur. Therefore, a detailed history plays a central diagnostic role. Exposure to fish tank or marine environment in combination with single or multiple skin nodules should raise suspicion of *M. marinum* infection.

In this case, TST became positive in the course of the disease. TST is considered to be specifically associated with *M. tuberculosis*, however, false positive tests due to non-tuberculous mycobacteria have been reported. Another recently published study showed evidence, that IGRA testing yields similar false positive results in discriminating between *M. tuberculosis* and *Mycobacterium avium* complex as TST. However, the significance of the change in the TST status of our patient remains unclear.

During the antibiotic therapy, which should be based on in vitro susceptibility tests, discontinuation of anti-TNF therapy is recommended. Monotherapy should be limited to patients with mild disease only. Clarithromycin combined with ethambutol or rifampicin seems to be the best combination therapy and should be continued for at least 1 or 2 months after the resolution of skin lesions. Recently, two cases of *M. marinum* infection in CD were reported, where anti-TNF therapy was reintroduced after completed anti-infective treatment. In both cases patients underwent incision and drainage of all nodules and were treated with minocycline for 6 months or with doxycycline for 3 months. In one case infliximab had been combined with azathioprine, because CD was again highly active three months after finishing minocycline therapy. Also, the second case resumed biologic therapy after stopping antibiotic therapy. In our case, up to now the anti-TNF therapy has been resumed for 12 months without recurrence of mycobacteria. However, no long-term outcomes have been published yet.

Several cases of *M. marinum* infections in transplant recipients have been reported. In these patients an immunosuppressive combination therapy had to be continued. Similar to our patient, the average duration of antibiotic treatment ranged from 3 to 6 months. In one case, a recurrence of skin lesions was reported, but successfully treated by reintroduction of antibiotic combination therapy.

4. Conclusion

Mycobacteriosis with *M. marinum* is a rare infection in patients with immunosuppressive therapy. This is the first case of a *M. marinum* infection in a patient treated with adalimumab for CD. Delay in diagnosis due to false negative PCR test and long-acting bacterial culture favors to local spread and infection of deeper structures. A history of contact with fresh or salt-water fish, swimming pools, or tropical aquaria is of great importance. The main prognostic indicator is the promptness of treatment. However, despite difficult and often delayed diagnosis, the clinical course of patients under anti-TNF treatment seems to be less aggressive than in patients receiving corticosteroids or anti-TNF combination treatment. Antibiotic therapy and sometimes local excision in addition to discontinuation of anti-TNF treatment is a successful therapeutic regimen. Reintroduction of anti-TNF therapy after the treatment is still under discussion but seems to be safe.

References


