Disseminated Mycobacterium marinum infection in a patient with rheumatoid arthritis receiving infliximab therapy

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Abstract
Tumor necrosis factor-α inhibitors are important adjunctive therapies for rheumatologic diseases. These agents increase the risk for granulomatous disease. We present a case of a woman with severe rheumatoid arthritis on infliximab who developed multiple nodular skin lesions. Biopsies grew Mycobacterium marinum. New lesions developed through therapy, necessitating surgical debulking.

Introduction
An increasing number of reports of infectious complications occurring in patients receiving anti-tumor necrosis factor-α (TNF-α) agents is being described. TNF-α is recognized as an important cytokine involved in the pathogenesis of many inflammatory conditions such as Crohn’s disease and rheumatoid arthritis (RA). The use of anti-TNF-α agents in treatment regimens of these patients is becoming more commonplace. Although all effects of TNF-α on the immune system are not completely understood, adequate levels seem to be required for an effective immune response to mycobacteria, granuloma formation and to inhibit bacterial dissemination. TNF-α blockade by an agent such as infliximab (Remicade), has been associated with increased reports of granulomatous infections, such as tuberculosis and non-tuberculous mycobacterial disease to a greater extent than other agents such as entanercept (Enbrel) [1]. A recently published meta-analysis of over 3000 RA patients on either infliximab or adalimumab showed a pooled odds ratio of 2.0 for serious infections (95% CI 1.3–3.1) [2]. A British prospective study of patients receiving anti-TNF agents also showed an increased rate of serious skin and soft tissue infections compared to RA patients taking traditional disease-modifying anti-rheumatic drugs (DMARDS) [3].

Mycobacterium marinum is an atypical mycobacterium that can cause infection when contaminated water (recreational aquatic activities, fish tanks, etc.) is exposed to traumatized skin. Cutaneous disease manifested as nodular or ulcerating skin lesions are typical in immunocompetent hosts, while disseminated infection such as tendon, bursae or bone involvement are more common, albeit rare, in immunocompromised persons. Delayed diagnosis and immune suppression contribute to invasive disease in immunocompromized hosts. M. marinum arthritis has been reported to mimic rheumatoid arthritis often leading to a delay in diagnosis [4]. Because patients with rheumatoid arthritis (RA) usually have joint symptoms at baseline, higher suspicion is needed for aggressive work-up to define appropriate management. Few reports exist on the clinical course and management of patients with mycobacterial disease related to TNF-α inhibitors. We present an unusual case of extensively disseminated M. marinum disease in a patient with RA, who
developed infection while receiving infliximab and describe the refractory nature of the disease and complicated management.

Description of the case

A 51 year old female with a 16-y history of rheumatoid arthritis involving primarily her wrists, hands and knees was refractory to multiple immunosuppressive medications over the past several y. Most recently, she had achieved control with methotrexate (22.5 mg weekly), meloxicam and infliximab infusions (7 mg/kg) every 6 weeks. The infliximab was begun in May 2003. A purified protein derivative test (PPD) was negative prior to start of infliximab therapy. She was referred to the infectious diseases clinic for the evaluation of persistent nodular skin lesions on her thighs and upper lip of 2 months duration and 2 weeks of intermittent fevers.

In February 2006, she had observed painless, dime-sized erythematous nodules on her bilateral upper thighs. Two weeks later, another painless lesion on the vermillion border of her lower lip was noted. She had a routine follow-up with her rheumatologist 1 week following the appearance of the buccal lesion and was referred for biopsies. Histopathological examination of the buccal mucosa and thigh lesions revealed superficial and deep granulomatous and histiocytic inflammation with special stains (Fite and Ziehl-Nielsen) positive for acid-fast bacilli. A repeat PPD was now positive at 26 mm, and a chest radiograph was normal. She was empirically treated for probable tuberculosis with rifampin, isoniazid, pyrazinamide and ethambutol pending culture results. Infliximab was discontinued.

Two weeks later, repeat biopsies of her lip and thigh lesions with cultures were performed. Herpes simplex virus and varicella zoster virus direct fluorescent antibody (DFA) were negative. Repeat biopsies confirmed previous histopathology and special stains were AFB-positive. The DNA probe for both M. tuberculosis and M. avium complex from tissue specimens was negative, and anti-tuberculous drugs (except isoniazid) were discontinued. Isoniazid was continued for the treatment of latent tuberculous infection. Of note, the patient recalled improvement of her lip lesion while on the 4-drug regimen.

Over the next 2 months, the patient subsequently noted a new tender right calf erythematous nodule and developed constitutional symptoms. She denied arthalgias, myalgias, visual changes, gastrointestinal symptoms or any known sick contacts. She had been managing her fevers with acetaminophen and continued to take meloxicam and methotrexate. Further history revealed no recent travel outside the Virginia area; however, she regularly vacationed in a cabin along the Shenandoah River. Her dogs swam in the river every weekend and frequently sat on her lap and licked her face. There were no other notable water exposures or trauma to skin. Physical examination revealed 2 anterior thigh nodules that showed evidence of previous central biopsy (Figure 1A) and an inflammatory and crusty marble-sized nodule on her lower (lip) labial border (Figure 1B). Her right gastrocnemius was tender and slightly erythematous, and also had a palpable and tender nodule. A complete blood count, chemistries and erythrocyte sedimentation rate were unremarkable apart from a hemoglobin of 11.9 g/dl. A repeat chest radiograph was normal. At that time, mycobacterial cultures of tissue from prior biopsies yielded M. marinum, and rifampin (600 mg daily) and ethambutol (25 mg/kg daily) were begun. Isoniazid was discontinued.

Figure 1. A) One of the patient’s initial dime-sized nodular, erythematous lesions on her left thigh following a central punch biopsy. B) The patient’s lower face and anterior neck illustrates a crusted, erythematous nodule on the vermillion border of the lower lip (upper arrow) and 3-mm erythematous papule (lower arrow).
In follow-up 3 weeks later, the patient’s physical examination was significant for increasing erythema and tenderness about her left distal humerus near the insertion of the medial epicondyle. A radiograph of the left elbow was normal. Her lip and thigh lesions were unchanged. A drug resistance panel confirmed sensitivities to her antimicrobials, and she reported compliance with the medications. Clarithromycin was added due to concerns of disease progression. Three weeks later, she noticed acute right knee pain and gradually increasing right thumb pain. Due to concerns of a RA flare, after consultation with her rheumatologist, low-dose prednisone (5 mg) was begun. In mid-May 2006, follow-up revealed an intensely swollen, tense and painful right calf and worsening left elbow pain. An ultrasound did not show evidence of deep venous thrombosis, but was significant for a 11.0 × 4.0 × 4.0 cm complex hypoechoic fluid collection within the posterolateral calf resembling either an abscess or ruptured Baker’s cyst. Needle aspiration was unsuccessful due to the viscosity of the material. Moxifloxacin was added to her other agents and prednisone was discontinued. Magnetic resonance imaging of her right calf revealed a rim-enhancing T2 hyperintense signal measuring 4.5 × 1.1 × 12.1 cm, abutting the fascia of the medial and lateral gastrocnemius consistent with a right calf fluid collection/abscess, as well as a fluid collection within her knee joint space with enhancement of the synovial margins. A MRI of her left elbow demonstrated a well-circumscribed T2 hyperintense 1.2 × 3.0 × 5.5 cm loculated fluid collection, consistent with an abscess, with cortical disruption of the humeral condyle suggestive of osteomyelitis. Progression of disease and the development of multiple large abscesses and osteomyelitis despite 3-drug therapy necessitated extensive surgical drainage and debridement of her left elbow and right calf abscesses and removal of her thigh lesions with the goal of reduction of her overall disease burden. Histopathology revealed osteonecrosis and osteomyelitis of the olecranon, marked inflammatory cell infiltration and granuloma formation. Bacterial, fungal and mycobacterial cultures were without growth. The lip lesion had resolved with therapy. She has continued 4-drug therapy. At return visits 1, 2 and 4 months later, the patient was free of new lesions and tolerating these medications. Her RA was increasingly difficult to control without prednisone and infliximab, so methotrexate and meloxicam were continued and sulfasalazine was later added.

**Discussion**

Infection with *M. marinum* is usually associated with aquatic activities in fresh water, salt water or marine life. In our unique case, the likely route of inoculation was through minor skin abrasions on the patient’s upper thighs from her dogs, which frequently swam in a river. Lesions tend to develop after initial traumatic injury or abrasions to the skin, and rarely spread to deeper tissue unless immunosuppression is present. The patient’s diagnosis and delay in initiation of therapy likely contributed to her extensive disease. Mycobacterial disease is often only considered after a patient has failed multiple courses of antibiotics [5]. Frequently, biopsies will not reveal organisms, and cultures are the mainstay for diagnosis but may result in a substantial delay in species identification. Because the incubation period can be quite variable, from 2 to 4 weeks up to 9 months, taking a detailed history of exposures in immunosuppressed patients is critical [6]. It is likely that the patient’s PPD conversion was related to her disseminated mycobacterial disease.

Treatment of extensive *M. marinum* disease in a rheumatoid arthritis patient receiving ongoing immunomodulating therapies can be challenging. Multicenter controlled trials are not available to help define optimal regimens for such patients. Extended lengths of therapy, beyond 12 months, are common. Examples include a case report describing a RA patient with cutaneous *M. abscessus* disease that was cured after 12 months of monotherapy with clarithromycin, and a review of 8 *M. marinum* arthritis cases noting the average duration of therapy was 8 months (range 3–12 months) [7,8]. While the optimal combination of therapy and duration is still not well defined, published studies suggest that preferred first-line regimens for disseminated disease include 2–3 medications: clarithromycin, rifampin and/or ethambutol. If continued cutaneous lesions or further joint involvement occurs, the use of second-line agents such as amikacin or streptomycin has resulted in clinical improvement [9]. The role of immunoglobulins has also been cited for disseminated *M. marinum* disease but has had mixed rates of success [10]. A suggestion for acquired resistance in this patient’s case was considered, as has been reported in the literature [11]. In our case, the isolate was sensitive to her 2 initial medications as well as the drugs added later in her treatment course. Noncompliance was not thought likely with this patient, and progression was likely due to multiple factors including immunosuppression, the burden of mycobacterial disease and poor penetration of antituberculous agents into her multiple abscesses. As in this case, surgery can be an important and necessary adjunct to therapy. However, series of cases managed surgically show that not all cases have
ultimate cure, but improvement in overall disease is usually seen [12–15].

In addition to placing infected patients on a reasonable antibiotic regimen, one should also consider modification of the patient’s immunosuppressive medications. Continued prednisone therapy at moderate dosing ranges, such as 15 mg/d, has been ascribed to treatment challenges in a patient with systemic lupus erythematosus [16]. If an anti-TNF-treated patient develops a serious infection, both the rheumatologist and the infectious diseases physician should decide which immunosuppressive medications should be stopped immediately and when and if the patient should restart the drug(s) after the infection has resolved. If the infection takes an extended period of time to cure or their underlying disease worsens mandating new RA medications, the patient should be considered ‘high risk’ and future anti-TNF-α therapy should be withheld. In this case, the patient did not receive further infliximab therapy following the appearance of her buccal lesion, but her infection progressed while she remained on methotrexate and a short course of low-dose prednisone.

Because chronic infliximab therapy can result in significant immunologic impairment, all physicians who manage patients on this drug, either for rheumatologic or gastrointestinal conditions, should counsel them about the increased risk of infection as well as cautions to limit exposure to freshwater environments. Dermatologists and rheumatologists, who often manage initial cutaneous M. marinum disease, should have a low threshold to obtain biopsies and cultures and refer for infectious diseases consultation early. Patients with M. marinum disease have been erroneously diagnosed with pyoderma gangrenosum, especially if cultures are not taken, and this misdiagnosis can expose patients to the risks of further immunosuppression and result in a delay in diagnosis. The laboratory should be notified of the suspicion for M. marinum, so that cultures are incubated at 30°C, has been ascribed to treatment challenges in a patient with systemic lupus erythematosus [16]. If an anti-TNF-treated patient develops a serious infection, both the rheumatologist and the infectious diseases physician should decide which immunosuppressive medications should be stopped immediately and when and if the patient should restart the drug(s) after the infection has resolved. If the infection takes an extended period of time to cure or their underlying disease worsens mandating new RA medications, the patient should be considered ‘high risk’ and future anti-TNF-α therapy should be withheld. In this case, the patient did not receive further infliximab therapy following the appearance of her buccal lesion, but her infection progressed while she remained on methotrexate and a short course of low-dose prednisone.

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