Case Report

Mycobacterium marinum infection complicated by anti-tumour necrosis factor therapy

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Mycobacteria other than tuberculosis infections in patients taking various tumour necrosis factor (TNF)- α inhibitors have been reported in the literature. We describe sporotrichoid spread of *Mycobacterium marinum* in a man with Crohn's disease treated with infliximab. After starting ethambutol and rifampicin and discontinuing infliximab, a worsening appeared. *M. marinum* infection may have a potential local spread and systemic dissemination in patients treated with TNF- α inhibitors.

Case report

A 32-year-old man was referred to our department because of cellulitis of the thumb on the right hand despite a course of cloxacillin and another of amoxicillin/clavulanic acid. His medical history included Crohn's disease since 1996. In September 2005, he had been started on infliximab infusions with an excellent clinical response. A tuberculin skin test performed before administration of infliximab was negative and a chest X-ray revealed no evidence of active or prior tuberculosis. After 6 months, the infliximab infusion was stopped. In September 2007, his disease worsened despite maintaining a background therapy that included prednisone (10 mg daily), mesalazine (1 g daily) and metronidazole (500 mg daily), and infliximab was added to the regimen. Six weeks after starting with the infliximab, he presented with skin lesions on his right thumb and forearm. He did not recall preceding trauma. He reported caring for fishes in a domestic aquarium. On physical examination, the thumb was erythematous and scaly, and there were two red and painful inflammatory papules on the distal forearm and multiple scattered subcutaneous nodules on the ipsilateral proximal forearm and distal arm with a sporotrichoid pattern (Fig. 1a). Regional lymphadenopathy was absent and a general examination was otherwise unremarkable. A biopsy was done. Microscopic examination of the skin biopsies revealed necrotizing and granulomatous inflammation. A Ziehl–Neelsen stain revealed many acid-fast bacilli, and a photochromogenic mycobacterium was grown in culture within 10 days. It was identified as *Mycobacterium marinum* by 16S rRNA gene sequencing methods.

Abbreviations: MOTT, mycobacteria other than tuberculosis; TNF, tumour necrosis factor.

Therapy with ethambutol, 1200 mg per day, and rifampicin, 600 mg per day, was started and infliximab was discontinued.

One month later, the skin lesion on the thumb had improved but the subcutaneous nodules on the forearm had increased markedly in size and new ulcerated lesions had appeared on the forearm. In addition, a sinus with purulent discharge had developed at the site of the distal lesion (Fig. 1b) from which *M. marinum* was cultured. At that time, clarithromycin, 500 mg twice daily, was added. Two months later, the size of the previous ulcerated nodules had decreased, but new red and ulcerated lesions had appeared on the previous nodules. No organisms were found by Ziehl–Neelsen staining of the pus from the new lesions, and culture on Löwenstein–Jensen medium did not grow organisms. Due to worsening of rectal symptoms, immunosuppressive therapy with 6-mercaptopurine (150 mg daily) was started. At month 3, new red suppurative lesions appeared over previously subcutaneous nodules. Ziehl–Neelsen stain and cultures of the pus for mycobacteria were again negative. The dose of prednisone was raised to 20 mg daily. At month 4, several nodules with scanty suppuration and a hard consistency were present (Fig. 1c). A Ziehl–Neelsen stain and cultures for mycobacteria were repeatedly negative. At month 7, only hard subcutaneous nodules and scars were seen without ulcerative or suppurative lesions. Rifampicin and ethambutol were stopped and clarithromycin was continued; prednisone was decreased to 10 mg. At month 10, only scars were present at the level of the previous suppurative lesions. However, a new red subcutaneous nodule appeared on the distal arm that drained scanty pus from which a Ziehl–Neelsen stain revealed some acid-fast bacilli, but

Fig. 1. (a) Erythematous and verrucous plaque on the thumb (at diagnosis); (b) painful, suppurative papules and nodules on the forearm (1 month after diagnosis); (c) several nodules with scanty pus discharge and a hard consistency (4 months after diagnosis).

cultures for mycobacteria were negative. Rifampicin and ethambutol were introduced again. Fortunately, at month 11, the lesion resolved. Susceptibility testing showed that the strains were sensitive to clarithromycin, rifampicin, ethambutol and ofloxacin. The antibiotic treatment was finally stopped at month 14 after diagnosis.

Discussion

Infliximab has been associated with an increased risk of tuberculosis (Keane *et al.*, 2001). This risk is less clear for infections caused by mycobacteria other than tuberculosis (MOTT) (Salvana *et al.*, 2007).

Tumour necrosis factor (TNF) has an important role in granuloma formation and maintenance (Ehlers, 2005). While the increased risk for reactivation of latent tuberculosis on treatment with TNF- α inhibitors is well described, less clear is the risk for MOTT infections (Salvana *et al.*, 2007). Wallis *et al.* (2004) reported 29 unspecified MOTT infections in 197 000 patients treated with infliximab and 113 000 with etanercept from the US Food and Drug Administration (FDA) adverse events reporting system. Recently, Winthrop *et al.* (2009) presented 239 reports of MOTT infection in patients who were receiving anti-TNF- α therapy recovered from the FDA postmarketing surveillance system (MedWatch database)

through 1 January 2007. These reports are not confirmed MOTT infections, as the reporting procedure might not be sufficient to fulfil the American Thoracic Society diagnostic criteria of MOTT infection (Griffith *et al.*, 2007).

Moreover, several case reports of MOTT infection developing in patients taking various TNF- α inhibitors have been recovered from the PubMed database. At least 12 species of MOTT have been described, including *Mycobacterium abscessus* (Mufti *et al.*, 2005), *Mycobacterium avium* (Salvana *et al.*, 2007), *Mycobacterium aurum* (Martín-Aspas *et al.*, 2008), *Mycobacterium chelonae* (Díaz *et al.*, 2008), *Mycobacterium fortuitum* (Boulman *et al.*, 2006), *Mycobacterium haemophilum* (Swart *et al.*, 2009), *Mycobacterium kansasii* (Malkin *et al.*, 2009), *Mycobacterium marinum* (Chopra *et al.*, 2002; Rallis *et al.*, 2007; Fallon *et al.*, 2008; Danko *et al.*, 2009; Dare *et al.*, 2009), *Mycobacterium mucogenicum* (Shehan & Sarma, 2008), *Mycobacterium peregrinum* (Marie *et al.*, 2005), *Mycobacterium xenopi* (Yim *et al.*, 2004) and *Mycobacterium szulgai* (van Ingen *et al.*, 2007). The main sites of infection were the pulmonary region and skin and soft tissue (Winthrop *et al.*, 2009). Cutaneous infections by MOTT have been caused mainly by *M. marinum* (Rallis *et al.*, 2007; Fallon *et al.*, 2008; Danko *et al.*, 2009; Dare *et al.*, 2009) and less commonly by *M. abscessus* (Mufti *et al.*, 2005), *M. chelonae* (Díaz *et al.*, 2008) and *M. mucogenicum* (Shehan & Sarma, 2008).

Table 1. Summary of the reported cases of *Mycobacterium marinum* infection in patients receiving TNF- α inhibitors recovered from PubMed

Reference	Sex, age in years	Underlying disease*	TNF- α inhibitor	Other immunosuppressive drugs	Delay from start of anti-TNF therapy to infection (months)	Clinical	Treatment†	Total duration (months)	Outcome	Worsening after starting treatment
Chopra <i>et al.</i> (2002)	M, 61	RA	Etanercept	No	8	Tenosynovitis (wrist)	CLA and surgery	3	Recovered	No
Fallon <i>et al.</i> (2008)	F, 37	AS	Infliximab	Azathioprine	24	Skin infection (lower extremity with sporotrichotic distribution)	DOX, CLA, RIF	NR	Recovered	No
Rallis <i>et al.</i> (2007)	M, 45	CD	Infliximab	No	7	Skin infection (upper extremity with sporotrichotic distribution)	RIF, ETB	8	Recovered	No
Dare <i>et al.</i> (2009)	M, 64	AS	Etanercept	No	12	Skin infection (upper extremity with sporotrichotic distribution)	SXT	12	Recovered	No
Danko <i>et al.</i> (2009)	F, 51	RA	Infliximab	Methotrexate	33	Skin infection, abscess and osteomyelitis	CLA, RIF, ETB, MOX and surgical drainage	NR	Recovered	Yes
This report	M, 32	CD	Infliximab	Prednisone	36	Skin infection (upper extremity with sporotrichotic distribution)	CLA, RIF, ETB	14	Recovered	Yes

NR, Not recorded.

*RA, rheumatoid arthritis; AS, ankylosing spondylitis; CD, Crohn's disease.

†CLA, clarithromycin; DOX, doxycycline; RIF, rifampicin; ETB, ethambutol; SXT, co-trimoxazole; MOX, moxifloxacin.

M. marinum causes diseases in many fish species and is distributed worldwide. Infection occurs by direct injury from fish fins or after cutaneous trauma and subsequent exposure to contaminated water (Piersimoni & Scarparo, 2009). An increasing number of cases in immunocompetent and immunodepressed hosts have been reported (Piersimoni & Scarparo, 2009; Pandian *et al.*, 2008). A presumptive identification can be made by production of photochromogenic pigment and a positive test for urease. However, a definitive identification involves reverse hybridization techniques or HPLC analysis of mycolic acids and DNA sequencing assays (Piersimoni & Scarparo, 2009).

Five previous cases of *M. marinum* infection in patients using TNF- α inhibitors have been reported in the literature (from January 2000 to October 2009) (Chopra *et al.*, 2002; Fallon *et al.*, 2008; Rallis *et al.*, 2007; Danko *et al.*, 2009; Dare *et al.*, 2009). A summary of these cases along with the case reported here is shown in Table 1. The first case report was a tenosynovitis on the wrist occurring in a patient with rheumatoid arthritis receiving etanercept (Chopra *et al.*, 2002). In three cases, the disease remained confined to the cutis on extremities with sporotrichotic distribution (Rallis *et al.*, 2007; Fallon *et al.*, 2008; Dare *et al.*, 2009). One case of disseminated *M. marinum* infection (cutaneous, abscess and osteomyelitis) was reported in a patient receiving infliximab (Danko *et al.*, 2009).

Our patient's course worsened clinically after stopping infliximab while on anti-*M. marinum* treatment, and *M. marinum* was isolated from a subcutaneous nodule after 1 month. After 1 month, occasional acid-fast bacilli were seen in many specimens, but cultures were negative for *M. marinum*. Danko *et al.* (2009) describe a case of cutaneous infection caused by *M. marinum* in which disseminated disease appeared 3 weeks after stopping anti-TNF therapy and starting a rifampicin and ethambutol therapy. Also a new lesion appeared after clarithromycin was added to the treatment. Cultures were negative for *M. marinum* after initiation of therapy. Our case and the case of Danko *et al.* (2009) illustrate that a potential local and systemic dissemination may be occurring in patients using anti-TNF therapy. Disseminated *M. marinum* infections have been reported in other immunocompromised patients such as transplant recipients (Pandian *et al.*, 2008) or a patient treated with oral corticosteroids (Streit *et al.*, 2006). The exact duration of antibiotic therapy for *M. marinum* infection is not defined in the anti-TNF therapy population, and should be individualized.

In conclusion, cutaneous infections with a sporotrichoid pattern of spread should raise the suspicion of *M. marinum* infection and a potential local spread and systemic dissemination during the treatment and after stopping TNF- α inhibitors.

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