Rapid growing mycobacteria and TNF-α blockers: case report of a fatal lung infection with *Mycobacterium abscessus* in a patient treated with infliximab, and literature review

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ABSTRACT

Rapid growing mycobacteria pose as a serious emerging threat for patients treated with TNF-α blockers.

We report a case of a progressive and fatal pulmonary infection with M. abscessus in a patient previously treated with infliximab for Crohn's disease and review seven other previously reported patients.

Five out of eight patients were female. The patients were treated with either anti-TNF-α antibodies or TNF-α blocking receptor. The diagnosis of RGM came in the first 6 months after initiation of TNF-α blockers in five out eight patients. The two patients with M. abscessus lung infection died in spite of antibiotic treatment, whereas the other patients with skin affection and lever affection due to M. Fortuitum had a resolution of their symptoms with discontinuation of TNF-α blockers and antibiotics.

Introduction

Infections due to non-tuberculous mycobacteria (NTM) and particularly rapidly growing mycobacteria (RGM) still remain unfamiliar even though they represent an emerging concern, especially for immunosuppressed patients. They are responsible for disseminated disease, pulmonary infection, lymphadenitis, skin and soft tissue infection, musculoskeletal infection and foreign body-related infection related to prosthetic devices and catheters.

RGM include three clinically relevant species: *Mycobacterium fortuitum*, *M. chelonae* and *M. abscessus*. RGM are ubiquitous both in the natural and man-made environment. Actual transmission to humans from an environmental source with subsequent clinical disease is rarely proven (1).

We report a case of a progressive and fatal pulmonary infection with *M. abscessus* in a patient previously treated with infliximab for Crohn's disease and review the literature.

Case report

The patient, a white woman born in 1960, had been a heavy smoker – about 1.5 packets of cigarettes daily – since 1976. Her relevant medical history included chronic obstructive pulmonary disease (COPD) and Crohn's disease since 1982 complicated with ileocaecal resection and whose exacerbations were treated with prednisolone as needed. Prior to infliximab treatment, the patient was assessed for latent tuberculosis infection clinically and with a chest x-ray. Neither a tuberculin skin test (TST) nor interferon gamma release assay (IGRA) was performed. She received a total of five infusions with infliximab 250 mg from February to September 2006. Infliximab treatment was interrupted because of several episodes of bronchitis and pneumonia.

The patient had lost 7 kg in the past year and weighed 38 kg for a height of 152 cm. She had episodes of fever, exertional dyspnoea, coughing with productive sputum without haemoptysis. Chest computed tomography showed at first small nodular shadows associated with lung fibrosis and thereafter caverns in both apical lobes in November 2007 (Fig. 1). A Fibre optic bronchoscopy

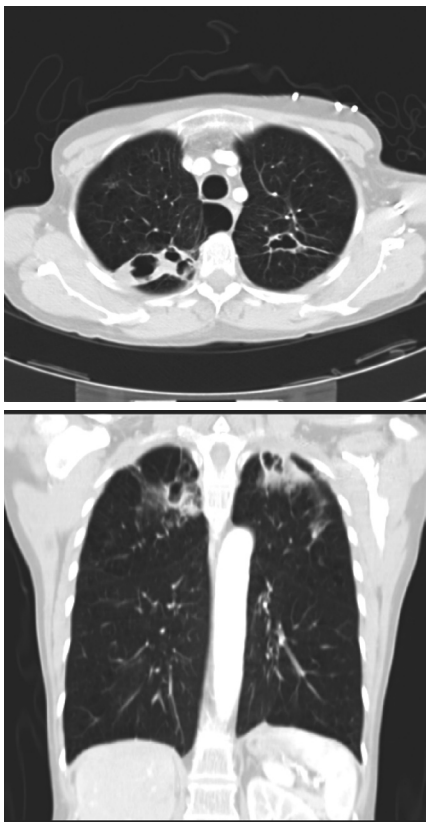

Fig. 1. Chest Computed Tomography before left upper lobectomi was performed, March 2008. Coronal and frontal planes with findings of caverns in both upper lobes.

Table I. Summary of reported data in 7 patients with RGM infection treated with TNF-α blockers.

Patients' characteristics	Possible risk factors	TNF-α blocker	Concomitant therapy	TNF-α blocker exposition	RGM Localisation	Infection characteristics	Antimicrobial treatment and duration	Outcome	Ref.
M, 56y, USA 11y-history of seropositive RA	RA lungs	Etanercept 2x25mg/w	Pred 2mg/d + LEF 20mg/d	15 mo	*M. abscessus* Lung	Pneumothorax. Parenchymal consolidation in multiple lobes on chest CT	Amikacin + Cefoxitin + Clarithromycin	Death 2 mo after diagnosed	[2]
F, 67y, Canada 6y-history of seropositve RA	Lower leg cast?	Infliximab 200mg/8w	Pred 7mg/d + MTX 20mg/w	14 mo	*M. abscessus* Skin	Red swollen lesion with small ulcer and draining sinuses at left lower thigh.	Clarithromycin 12 mo	Resolution	[3]
F, 73y, Israel 20y-history of seronegative RA	None	Infliximab 3mg/kg	MTX 15mg/w	3 mo	*M. fortuitum* Liver	Rising liver enzymes	Ciprofloxacin 3 mo	Resolution	[4]
F, 70y, France 30y-history of seropositive RA	None	Etanercept 50mg/w Worse under Adalimumab 40mg eow	Pred 8mg/d + MTX 10mg/w	5mo	*M. chelonae* Skin	10 papulo-nodular purplish lesions at the right leg	Amoxicillin-Clavulanic acid + tigecyclin 16 w	Resolution	[5]
M, 68y, France Vasculitis secondary to myelodysplasia	Skin (purpura, livedo) Diabetes	Infliximab Dose?	NR	2 mo	*M. chelonae* Skin	2 inflammatory nodules in thigh and upper arm	Amikacin + Clarithromycin for 3w; then Clarithromycin	Resolution	[6]
F, 68y, Spain 10y-history of seropositve RA	None	Adalimumab 40mg eow	Pred 10mg/d	2 mo	*M. chelonae* Skin	Multiple red tender subcutaneous nodules at lower limbs	Clarithromycin for 7 mo	Resolution	[7]
M, 66y, France 10y-history of SpA	None	Infliximab, switched to Adalimumab	NR	Over 36 mo	*M. chelonae* Skin	Inflammatory painless infiltrated nodules over right finger	Clarithromycin for 5 mo	Resolution	[8]
F, 46y, Norway 25y-history of Crohn's disease	COPD Low weight	Infliximab 250 mg/ 5 infusions	Pred as needed	5 mo	*M. abscessus* Lung	Pneumonia. Progressive chest findings: small noduli, lung fibrosis to abscess formation in upper lobes	Amikacin+ Linezolid+ Clarithromycin for 12 w. Lobectomy of right upper lobe. Clarithromycin+ Amikacin / Levofloxacin	Cachexia Hearing loss Respiratory failure Death, 17 mo after diagnosed	Present case

M: male; F: female; y: year; mo: month; w: weekly; d: daily; eow: every other week; MTX: methotrexate; Pred: prednisolone; RA: rheumatoid arthritis; SpA: spondyloarthropathy; COPD: congestive obstructive pulmonary disease; CT: computerised tomography; NR: not reported.

with bronchoalveolar lavage identified *Mycobacterium abscessus*.

The patient was treated according to sensitivities of the antibiogramme and relevant literature with per os clarithromycin 500 mg twice a day, linezolid 600 mg twice a day and intravenous amikacin (15 mg/kg) from the end of November 2007. After 12 weeks of treatment with antibiotics, a planned right upper lobectomy was performed. The biopsy of the lung specimen found numerous white nodular lesions corresponding to granulomatous inflammation and necrosis with acid-alcohol fast bacilli. The post-operative period was complicated with an unrecognised inferior myocardial infarction, an acute cholestasis and pulmonary superinfection with *Stenotrophomonas maltophilia*.

The patient's health worsened. Her weight decreased to 34 kg. She had episodes of respiratory failure and required supplemental oxygen. She developed hearing loss following the use of amikacin. In January 2009 after a new episode of pneumonia and respiratory failure that necessitated ventilatory assistance, the patient developed acute cholescystitis with secondary disseminated intravascular coagulation, and died.

Discussion

Seven other patients associating TNF-α blockers and RGM infections were identified in the review of the literature (2-8) (Table I). One patient treated with etanercept for psoriatic arthritis was disregarded as the patient developed endophtalmitis due to *M. chelonae* as a consequence of cataract surgery (9).

Five patients out of eight had rheumatoid arthritis (RA); five patients were female with a median age of 67.5 years. Most patients had concomitant treatments, such as methotrexate and-prednisolone, which are potential confounding factors. Both anti-TNF-α antibodies and TNF-α blocking receptor could be associated with RGM infection. Five out of eight patients were diagnosed with RGM infection less than 6 months after starting TNF-α blockers. This could argue in favour of reactivation of a latent infection.

Including the present case, there are only two reported patients with lung affection; both were infected with *M. abscessus* and died in spite of antibiotic treatment. They had a younger age at disease onset and had significant risk factors for lung disease with RA lungs for one (2) and COPD for the present case. Whereas the five patients with skin affection and one patient with lever affection secondary to *M. fortuitum* had resolution of their symptoms with discontinuation of TNF-α blockers and antibiotics.

An analysis of 105 patients with TNF-α blockers and NTM disease – 20 patients with RGM infections – from the United States Food and Drug Administration Medwatch database found similar characteristics: most of the patients were elderly women with RA, nearly-half of the patients with extra-pulmonary disease, with a median time between TNF-α blockers and infection of 18 weeks for adalimumab, 35 weeks for etanercept and 43 weeks for infliximab (10). The outcome remains largely unknown as less than 10% of the patients died by the time their cases were reported (10). Nevertheless, one could suspect that a greater number of deaths would occur during follow-up (10).

The diagnosis of NTM/RGM infections should always be based on the potential virulence of the NTM/RGM isolated, the host from which the organism is isolated and the source of the clinical specimen from which the NTM/RGM is isolated (11).

Risk factors include previous lung diseases and immunosuppression because of drugs, genetic predisposition and HIV (1). RGM lung infection can also be found in non-smoking white female with a specific morphotype (12). Female sex seems to be an important risk factor. This fact is illustrated in two very different studies: 84% of patients treated for *M. abscessus* lung disease are female in the study of Jeon *et al*. (13), and 83% of patients treated with lung resection for Nontuberculous disease (48 out of 236 patients had RGM infection) are female in the study of Mitchell *et al*. (14).

This case report and the associated literature review illustrate that NTM/RGM infections are an increasing concern in patients treated with TNF-α blockers. Cassidy *et al*. report that the prevalence of NTM disease with lung affection is more than double the prevalence of tuberculosis in Oregon (USA) although NTM infections are not systematically reported (15). The prevention of tuberculosis reactivation in patients with a rheumatic disease prior to TNF-α blockers has been successful; but prevention against NTM/RGM infections has yet not been addressed.

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