Case Report

Pleural effusion in an immunocompetent woman caused by *Mycobacterium fortuitum*

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Mycobacterium fortuitum is a non-tuberculous mycobacterium that can cause pneumonia, abscess and empyema in subjects with predisposing lung diseases. However, pleurisy with effusion is rare. Herein, we report the case of a 74-year-old immunocompetent female patient without apparent risk factors, who suffered haemorrhagic pleural effusion as the main clinical manifestation. Pleural nodules were detected by computed tomography scan, and microbiological analysis revealed *M. fortuitum* in the absence of other pathogens. The patient was treated with ceftriaxone and ciprofloxacin, and full recovery ensued in 4 weeks. To our knowledge, this is the first reported case of haemorrhagic pleural effusion in an immunocompetent patient without underlying diseases. Although non-tuberculous mycobacterial infections are rarely accompanied by pleural involvement, *M. fortuitum* should be considered in such cases, especially when microbiology fails to detect the usual pathogens, and when the clinical picture is unclear.

Received 30 July 2010
Accepted 29 March 2011

Introduction

Non-tuberculous mycobacteria (NTM) are widespread in the environment, particularly in the soil, water, dust and food. They can also be detected in the faeces of many animals. Classification of these organisms based upon colony morphology and growth characteristics was provided by Runyon (1959). According to this system, *Mycobacterium fortuitum* is one of the rapid-growing mycobacteria, and the *M. fortuitum* group is a group of pathogens containing *M. fortuitum*, *Mycobacterium peregrinum* and an unnamed third biovariant complex. Recently, additional species, including *Mycobacterium houstonense* and *Mycobacterium boenickei* and others, have been described within this group of organisms (Griffith *et al.*, 2007).

M. fortuitum was initially identified in the skin lesions of a patient in 1938 (Freeman, 1938), although it had first been isolated in a turtle in 1905. Data regarding the incidence of *M. fortuitum* infection are still under investigation.

The pathogenicity of such an organism depends on the opportunity for transmission and the susceptibility of the host. Humans usually acquire the disease-causing organism from environmental exposure, and no evidence of person-to-person spread of this infection has been documented (Woods & Washington, 1987), although infection can be transmitted by animal bites.

The clinical manifestations of *M. fortuitum* infections are cutaneous lesions, typically following trauma or clinical procedures, corneal keratitis, post-traumatic ulcers and lung disease, in individuals with underlying disorders (Sarma & Thakur, 2008; Lee *et al.*, 2010). In patients with genetic or acquired immunological defects, such as patients with human immunodeficiency virus (HIV) or those undergoing immunosuppressive therapy, *M. fortuitum* infection appears to be more frequent (Sack, 1990; Smith *et al.*, 2001). In addition, *M. fortuitum* infection is recognized as a nosocomial disease, and can occur in a hospital setting following injection: invasive procedures such as videoscopes and bronchoscopy; dialysis; use of central venous or other types of catheter; or after plastic, cosmetic, or cardiac surgery (Griffith *et al.*, 2007). Herein, we report a case of *M. fortuitum* infection in an elderly immunocompetent woman without apparent risk factors, who suffered pleural effusion as the main clinical manifestation.

Case report

In December 2008, a 74-year-old woman was admitted to University Hospital St Anna complaining of fever, chills and a dry cough. The patient reported no haemoptysis, weight loss or ongoing medication, and her medical history was negative. She was employed in a music shop and had no pets at home.

Abbreviations: CT, computed tomography; HIV, human immunodeficiency virus; NTM, non-tuberculous mycobacteria.

On admission, her temperature was 38.9 °C, her heart rate was 97 beats min⁻¹, her blood pressure was 120/70 mmHg and her resting oxygen saturation was 91 % with room air. Chest examination revealed dullness in the left hemithorax, without lymphadenopathy of the neck or supraventricular regions. Physical examination of the other organs was unremarkable. Her white blood cell count was 14 010 cells µl⁻¹ (80 % neutrophils), and her haemoglobin, platelet count, serum electrolytes, renal function and urinalysis were normal. Her erythrocyte sedimentation rate was 108 mm h⁻¹, and C-reactive protein level was 19.8 mg dl⁻¹ (reference range in our laboratory: 0.5–1.0 mg dl⁻¹). Blood cultures were negative for common pathogens, mycobacteria and fungi. An HIV assay for HIV-1 and HIV-2 (consent was obtained from the patient) was negative. The patient's absolute CD4⁺ cell count was 580 cells µl⁻¹, whereas her CD8⁺ lymphocyte counts displayed no abnormal values. A tuberculin skin test was negative. A QuantiFERON TB GOLD test (Geneticlab) was negative for latent *Mycobacterium tuberculosis* infection. Chest radiography showed bilateral pleural effusion, which was more evident on the left side than on the right (Fig. 1). Thoracentesis was performed, and 1550 ml haemorrhagic fluid was drawn off. The fluid contained 1840 white blood cells µl⁻¹, 220 U lactate dehydrogenase l⁻¹, 4.1 g protein dl⁻¹ and 2.2 g albumin dl⁻¹. A computed tomography (CT) scan of the chest showed minimal left and right pleural effusion, and nodules (diameter 4.07–7.35 mm) under the pleura on the left side (Fig. 2). Pleural biopsy was therefore performed on the left side, revealing massive lymphocyte and plasma cell infiltration, as well as proliferation of mesothelial cells. Cultures performed on pleural fluid aspirated by thoracentesis were negative for pyogenic germs and fungi. *M. tuberculosis* was not identified during routine microbiological examinations,

Fig. 1. Chest radiograph showing bilateral pleural effusion more evident on the left than on the right side (black arrow). The heart appears to be enlarged in its right and left profile.

Fig. 2. CT scan of the chest showing pleural fluid (white arrow) and nodules (diameter 4.07–7.35 mm) in the left posterior basal area under the pleura (black arrow).

which included Ziehl–Neelsen staining. However, culture of pleural fluid in a referral microbiology laboratory yielded rapid-growing mycobacteria after incubation in a radiometric automated Bactec culture system (Becton Dickinson). The isolate was confirmed as *M. fortuitum* based on its: growth in *p*-nitrobenzoic acid and MacConkey's agar; inability to form any pigment on Löwenstein–Jensen medium; tolerance to 5 % NaCl; positive nitrate reduction; and positive arylsulfatase test. Tests of antimicrobial sensitivity to different antibiotics, including anti-tuberculous drugs, were performed by the Kirby Bauer disc diffusion method on Mueller–Hinton agar, and the strain was found to be sensitive to cephalosporins, amikacin, ciprofloxacin, clarithromycin and imipenem (Table 1).

Table 1. Antimicrobial susceptibility testing for isolated *M. fortuitum*

Drug	Concentration (µg ml ⁻¹)	Result	
		Sensitive	Resistant
Isoniazid	>32	–	X
Ethambutol	>32	–	X
Rifampicin	>32	–	X
Streptomycin	>32	–	X
Amikacin	1	X	–
Cefoxitin	0.8	X	–
Ciprofloxacin	0.10	X	–
Clarithromycin	0.12	X	–
Doxycycline	>32	–	X
Imipenem	1	X	–
Linezolid	2	X	–

Treatment with cephalosporins (ceftriaxone 2 g, intravenously, once daily) and ciprofloxacin (200 mg, e.v, twice daily) was initiated and maintained for 4 weeks. The patient's symptoms disappeared without further treatment. A new chest CT scan showed no abnormalities. Close follow-up by our outpatient service for more than 1 year revealed no radiographic chest abnormality, and no relapse occurred.

Discussion

Over a 10 year period, from 1996 to 2005, *M. fortuitum* was identified in 25 (7.9%) of 317 cultures from clinical specimens positive for NTM (Pedro *et al.*, 2008). However, *M. fortuitum* infrequently causes pulmonary disease and basal pleural disease with effusion is rare, despite the fact that *M. fortuitum* is often described as a commensal pathogen of the respiratory tract (Hand & Sanford, 1970). *M. fortuitum* in the pulmonary tissue can, however, cause pneumonia, empyema (Wallace *et al.*, 1985) and abscess (Vadakekalam & Ward, 1991), although, when pulmonary infection occurs, it is usually superimposed onto a pre-existing lung disease, such as tuberculosis (Ichiyama & Tsukamura, 1987; Nussbaum & Heseltine, 1990); bronchiectasis, cystic fibrosis, pneumoconiosis or pulmonary alveolar proteinosis (Wallace *et al.*, 1983); chronic obstructive pulmonary disease (Lessing & Walker, 1993); exogenous lipid pneumonia (Jouannic *et al.*, 1996); or parapneumonic pleurisy (Smith *et al.*, 2001). One case of renal infection by *M. fortuitum* was described by Serra *et al.* (2007).

The case described herein supports the role of *M. fortuitum* in causing pleurisy with effusion, and leads us to make the considerations detailed below. First, in our patient, blood cultures for mycobacteria were negative, but *M. fortuitum* was subsequently cultured from pleural fluid and identified in a referral microbiology laboratory by biochemical methods. The identification of *M. fortuitum* was unsurprising, as positive blood cultures have been reported mainly in patients with impaired cellular immunity and AIDS, or those receiving glucocorticoid therapy, as *M. fortuitum* frequently causes disseminated infections (Sack, 1990; Smith *et al.*, 2001; Spell *et al.*, 2000).

Although a good standard protocol for the *Mycobacterium avium*–*Mycobacterium intracellulare* complex has not yet been established, classic microbiological culture and liquid culture-based mycobacterial detection systems, such as the Bactec system, remain a mainstay for the diagnosis of mycobacterial infections as they still have good potential in the diagnostic work-up of and therapeutic approach to these increasingly common infections (Griffith *et al.*, 2007; Serra *et al.*, 2007). The Bactec system, in particular, has become commonplace in clinical laboratories, offering the advantages of automation and shorter detection times from clinical samples.

Recently developed molecular techniques using amplified DNA and probe hybridization are also useful for direct and rapid identification of NTM species, but their overall cost

is high. Moreover, a number of molecular methods are research tools and not widely available, and the currently available kits are limited to the identification of a few species, and may not be useful in ruling out the disease (Pai & Ling, 2008). In addition, pleural fluid is a poor source of mycobacteria, and the levels of DNA present in such fluid are so low that a given aliquot may not contain an amplifiable target (De Lasseance *et al.*, 1992).

Second, in the case described, the pleural fluid was haemorrhagic, and CT scans showed subpleural nodules. As cytology for malignant cells was negative in both pleural effusion and biopsy lesions, and because no trauma, pulmonary embolization, haematological disorders or endometriosis were found, we suspect that *M. fortuitum* could have a role in the production of the observed haemorrhagic fluid.

To our knowledge, this is the first case of haemorrhagic pleurisy caused by *M. fortuitum* in an immunocompetent patient, although rare cases of pleuritis with massive non-haemorrhagic pleural effusion caused by the *Mycobacterium avium*–*Mycobacterium intracellulare* complex, or thoracic empyema by *Mycobacterium chelonae*, have been described in non-compromised women (Yanagihara *et al.*, 2002; Hsieh *et al.*, 2008). Thus, NTM should henceforth always be included in the differential diagnosis of a patient with pleural exudate, whether it be haemorrhagic or not, small or massive (Sarma & Thakur, 2008; Polverosi *et al.*, 2010), and especially when microbiology fails to detect the more usual pathogens.

Third, the patient clinically recovered 1 month after starting therapy. The optimal choice of agents is unknown, and is likely to depend on patient tolerance; however, any two-drug combination based on *in vitro* susceptibility should be successful (Griffith *et al.*, 2007). In our patient, *M. fortuitum*, as are most rapidly growing NTM, was resistant to conventional anti-tuberculous drugs, but was sensitive to a number of other agents, including cephalosporins and fluorinated quinolones.

The combination of two drugs has been shown to be therapeutically successful over a short period of time. In this setting, the relative effectiveness of dual agent therapy with respect to monotherapy, and the optimal duration of antibiotic therapy are unknown (Winthrop *et al.*, 2004). Atypical *M. fortuitum* infections from non-immunocompromised and non-HIV positive patients have been successfully treated for 3–4 weeks or even for 2 weeks with no evidence of recurrence (Ding *et al.*, 2006; Serra *et al.*, 2007; Sarma & Thakur, 2008). However, some authors have treated patients with consistent immunodeficiency due to AIDS for a total of 6 weeks (Spell *et al.*, 2000).

NTM are rarely accompanied by pleural involvement, especially in the absence of predisposing conditions. Nevertheless, *M. fortuitum* should be suspected, especially when the usual pathogens are not detected and when the clinical picture is unclear.

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