**Case Report**

**Mycobacterium abscessus** prosthetic valve endocarditis in a patient with Marfan syndrome

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**Introduction:** Mycobacterium abscessus is a non-tuberculous mycobacterium ubiquitous in the environment, which rarely causes endovascular infections. We report the first published case, to the best of our knowledge, of *M. abscessus* endocarditis in a patient with Marfan syndrome.

**Case presentation:** A female in her 40s with a history of Marfan syndrome status-post mechanical aortic valve replacement and a chronic indwelling venous access port presented with a 2-day history of confusion and 3-month history of intermittent fevers. Her blood cultures grew *M. abscessus*. An echocardiogram revealed a 1 cm vegetation attached to the prosthetic aortic valve and a perivalvular abscess. The patient was started on imipenem/cilastatin, amikacin and linezolid. Her course was complicated by septic emboli to the brain and subarachnoid haemorrhage. She was deemed a poor surgical candidate. The patient ultimately developed cardiac arrest and died.

**Conclusion:** *M. abscessus* endocarditis is rare and is associated with high mortality. Late recognition of *M. abscessus* as a causative pathogen of endovascular infection, extensive antimicrobial resistance and limited surgical options at the time of diagnosis make the management of *M. abscessus* endocarditis very challenging.

**Keywords:** amikacin; imipenem/cilastatin infective endocarditis; linezolid; Marfan syndrome; non-tuberculous mycobacteria.

**Introduction**

*Mycobacterium abscessus* was first recognized as a pathogenic mycobacterium in 1953 when it was identified as the causative agent of a traumatic knee infection and soft tissue abscess (Moore & Frerichs, 1953). *M. abscessus* was initially considered a subspecies of *Mycobacterium chelonae*, but subsequent DNA analyses led to its recognition as a separate species (Wallace, 1994). Similar to other non-tuberculous mycobacteria (NTM), *M. abscessus* is ubiquitous in the environment and can be isolated from soil, natural water and tap water from municipal water supplies. In humans, *M. abscessus* has been associated with a variety of clinical syndromes including skin and soft tissue infections with abscess complications, pneumonia and pulmonary nodules, osteomyelitis, meningitis and disseminated infection. *M. abscessus* accounts for more than 80% of pulmonary infections caused by rapid growing mycobacteria (RGM) (Griffith et al., 2007). RGM encompasses a group of mycobacteria that form mature colonies on solid agar within 7 days (Runyon, 1959). While growth takes longer than common Gram-positive and Gram-negative organisms, it is faster than other species of mycobacteria. It is the third most common cause of pulmonary infections due to NTM only after *Mycobacterium avium intracellulare* and *Mycobacterium kansasii*. Outbreaks of *M. abscessus* have been described in the setting of contaminated injections and surgical supplies (Furuya et al., 2008; Koh et al., 2010). Severe *M. abscessus* infection is an increasingly recognized problem among transplant patients and persons with diverse immunosuppressive conditions (Morales et al., 2010; Bello et al., 2012; Richey et al., 2013).

*M. abscessus* is a rare cause of endovascular infections. Here, a case of prosthetic valve endocarditis due to *M. abscessus* in a woman with Marfan syndrome is presented.
Case report

A female in her 40s from rural Kentucky presented to our institution with new-onset confusion of 2 days duration. The patient also reported intermittent fevers and chills within the past 3 months for which she had been evaluated multiple times in different local emergency departments. The patient was known to have a history of Marfan syndrome complicated by aortic insufficiency requiring aortic valve replacement with a mechanical valve 10 years prior. The patient was on a stable dose of warfarin. She had a history of pulmonary emphysema related to Marfan syndrome and mediastinal adenopathy diagnosed by biopsy in 2005 as a benign granulomatous process of unknown aetiology.

Twenty-five days prior to presentation, the patient was admitted to a local hospital where she was found to have a 1 cm vegetation attached to her prosthetic aortic valve. An initial blood culture grew Staphylococcus hominis and M. abscessus. Serial repeat bacterial blood cultures were negative during this admission. The patient had a chronic indwelling venous access port for routine venous blood sampling, which was removed during the admission as this was considered a potential infectious source. The patient received vancomycin and meropenem, and was discharged on empiric intravenous vancomycin and ceftriaxone via an upper extremity peripherally inserted central catheter, in addition to oral rifampicin, with plans for a repeat echocardiography on follow-up.

Eleven days after hospital discharge, the patient presented to our institution. The patient was noted to be lethargic and in mild respiratory distress. Blood pressure was 96/58 mmHg, heart rate was elevated at 112 beats min\(^{-1}\) and in mild respiratory distress. Blood pressure was subsequently developed cardiac arrest and died.

Discussion

M. abscessus has been associated with a variety of clinical syndromes including skin and soft tissue infections with abscess complications, pneumonia and pulmonary nodules, osteomyelitis, menigitis and disseminated infection. This patient had a history of having a chronic indwelling venous access port, which may have been the port of entry for her M. abscessus endovascular infection. Bacteremia due to M. abscessus is rare and has been associated with intravenous drug use, the presence of indwelling vascular catheters, haemodialysis and immunosuppression.
Two cases of pacemaker infection due to *M. abscessus* have been reported (Cutay *et al.*, 1998; Kessler & Kourtis, 2004). Only 12 cases of endocarditis due to *M. abscessus* were identified via a Medline search. Four additional cases of endocarditis due to *M. chelonae* were reported prior to the recognition of *M. abscessus* as a separate mycobacterial species, and therefore these could also represent *M. abscessus* cases. Among these 16 cases, seven (43 %) involved prosthetic valve infection. The associated mortality was very high (11 cases; 69 %), despite surgery and prolonged antimicrobial therapy (Altmann *et al.*, 1975; Repath *et al.*, 1976; Levy *et al.*, 1977; Viscidi *et al.*, 1982; Wallace *et al.*, 1983; Rumisek *et al.*, 1985; Galil *et al.*, 1996; Liebeskind *et al.*, 2001; Tsai *et al.*, 2008; Al-Benwan *et al.*, 2010; Morimoto *et al.*, 2010; Williamson *et al.*, 2010; Garcia *et al.*, 2014; Huth *et al.*, 2015; Mahajan *et al.*, 2015).

To the best of our knowledge, this is the first case of *M. abscessus* endocarditis in a patient with Marfan syndrome. Marfan syndrome has been associated with increased transforming growth factor-β (TGF-β) signalling (Cañadas *et al.*, 2010). TGF-β suppresses cell-mediated immune responses by decreasing the production of IFN-γ, thus inhibiting the proliferation and differentiation of T-helper cells and activation of macrophages. Increased circulating TGF-β would ultimately decrease the activation of macrophages necessary for the immune response against mycobacterial infection. A recent study reported increased levels of TGF-β and reduced levels of IFN-γ in patients with pulmonary NTM compared with uninfected control subjects after ex vivo stimulation with *M. avium intracellulare*. The authors of the study postulated that their findings could be explained by an as-yet-unrecognized condition related to Marfan syndrome, as suggested by the marfanoid body habitus commonly seen among persons who develop pulmonary NTM and the similar abnormal immune responses observed in these patients (Ovrutsky *et al.*, 2013). We were unable to measure TGF-β or IFN-γ production in our patient; however, it is possible that these levels could have been abnormal in the setting of Marfan syndrome and therefore may have contributed to the initial pathogenesis. However, her history of granulomatous mediastinal adenopathy suggested a chronic, cell-mediated immune process and supports the proposed TGF-β-mediated mechanism putting Marfan syndrome patients at increased risk of mycobacterial infection.

On Gram staining, *M. abscessus* can be confused with diphtheroids or other Gram-positive rods. It can grow in routine bacterial culture medium and, similar to other RGM, *M. abscessus* usually grows within 7 days of culture incubation. Molecular techniques such as PCR of the 65 kDa heat-shock protein gene and restriction enzyme analyses can be used for rapid identification of this mycobacterium (Ringuet *et al.*, 1999).

Use of antimicrobial susceptibility testing to guide therapy against *M. abscessus* is confounded by limited correlation between *in vitro* testing results and *in vivo* clinical efficacy. Currently, the Clinical Laboratory and Standards Institute recommends broth microdilution for determination of *M. abscessus* breakpoints. Performing an E-test to determine breakpoints is not recommended due to trailing end points, unreliable reproducibility of results, which often have MICs higher than those determined by broth microdilution, and lack of a quality-control standard (Woods *et al.*, 2000; Brown-Elliott *et al.*, 2012). Whereas E-tests can be set up on agar discs in an institution’s microbiology laboratory, custom broth microdilution trays must be sent to commercial laboratories that are familiar with mycobacteria samples.

The treatment of invasive *M. abscessus* infections usually requires prolonged combination therapy with two or three active drugs. *M. abscessus* is resistant to standard anti-tuberculous drugs and other antimicrobials used against other NTM. Aminoglycosides and macrolides have been established as the main therapeutic agents. Acquired resistance to aminoglycosides has been reported, especially among cystic fibrosis patients with frequent prior exposure to aminoglycosides. *M. abscessus* possesses one copy of the rRNA operon that is targeted by aminoglycosides. Resistance is due to an adenosine to guanine mutation in the 16S rRNA gene that can occur after aminoglycoside exposure (Prammananan *et al.*, 1998). Macrolide resistance through inducible expression of the *erm* gene in *M. abscessus* subsp. *abscessus* has been well documented in up to 75 % of these cases (Nash *et al.*, 2009). Most *M. abscessus* isolates are resistant to cefoxitin, doxycycline and quinolones. Susceptibility to linezolid and imipenem is variable. Wallace *et al.* (2001) at the University of Texas tested the susceptibility of 98 clinical *M. abscessus* isolates to linezolid, and only 48 % of isolates were susceptible with a MIC of ≤16 μg ml⁻¹. Another study of 43 clinical isolates of *M. abscessus* isolated in Europe demonstrated that 83 % of isolates had intermediate MICs to imipenem of 8–16 μg ml⁻¹ (Lavollay *et al.*, 2013). Resistance of mycobacterium to linezolid and other β-lactam antimicrobials is mediated through alterations in penicillin-binding proteins and production of β-lactamases. *M. abscessus* can form peptidoglycans by an alternate mechanism from the traditional penicillin-binding proteins and has genes that encode nine different class B β-lactamases (Lavollay *et al.*, 2011). Complicated cases of macrolide-resistant *M. abscessus* strains usually require a combination of parenteral drugs based on *in vitro* MICs and consultation with experts in *M. abscessus* infections (Brown-Elliott *et al.*, 2012).

Because of limited antimicrobial options against *M. abscessus*, surgical treatment should be considered in an attempt to eradicate the source of infection and to maximize the chances of cure. Unfortunately, most of these cases are diagnosed at an advanced stage and surgery is not always feasible. Recognition of *M. abscessus* as a potential real pathogen when isolated from blood cultures, especially among recipients of prosthetic valves, would...
allow timely administration of antimicrobials and consideration of early surgical intervention, which may result in improved outcomes.

References


