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 with new-onset confusion of 2 days duration. 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 respiratory rate was 22 breaths min⁻¹. Her temperature was 101.5 °F. A loud systolic murmur best heard in the right upper sternal border was present on cardiac examination. Neurological examination revealed an arousable patient oriented in person, time and place. There were no meningeal signs and no focal motor or sensory deficits. A cell blood count revealed pancytopenia (white blood cell count of 3300 μl⁻¹ with 88 % neutrophils and 6 % lymphocytes, haemoglobin of 6.7 g dl⁻¹ and a platelet count of 124 000 μl⁻¹). A chemistry panel revealed mild hyponatraemia of 133 nmol l⁻¹ and normal kidney function and liver enzymes. Albumin was 1.4 g dl⁻¹. The international normalized ratio (INR) was subtherapeutic at 1.2. A human immunodeficiency virus ELISA test was negative. A chest-X-ray showed bibasilar opacities. Head computed tomography was negative for an acute process. A lumbar puncture was planned but the patient refused. Transthoracic echocardiography confirmed the presence of a 1 × 0.5 cm vegetation attached to one of the leaflets of the mechanical valve. Vancomycin, gentamicin, piperacillin-tazobactam and levofloxacin were started for empiric coverage of presumed bacterial endocarditis and possible pneumonia. The patient’s lethargy and haemodynamic instability rapidly resolved but the fever continued despite broad-spectrum antimicrobials. Her white blood cell and platelet counts normalized. Red blood cell transfusions were given for her normocytic, normochromic anaemia without evidence of haemolysis. The patient also received a heparin drip due to her subtherapeutic INR.

After 4 days of incubation, bacteria resembling Gram-positive rods were identified from admission blood cultures. In light of these results and prior culture data, *M. abscessus* prosthetic valve endocarditis was suspected. Drug resistance testing by broth microdilution of the prior *M. abscessus* isolate indicated that this isolate was resistant to macrolides, quinolones, tetracyclines and trimethoprim/sulfamethoxazole, and intermediate to cefoxitin. The MIC to amikacin was 16 μg ml⁻¹ (susceptible) and MICs to imipenem and linezolid were 8 and 16 μg ml⁻¹, respectively (intermediate resistance). After discussing available antimicrobial options with experts at the National Jewish Hospital in Denver, CO, the regimen was switched to imipenem/cilastatin 1 g intravenously given over 3 h extended infusions every 6 h, amikacin 15 mg kg⁻¹ intravenously every 24 h and linezolid 600 mg orally every 12 h. Cardiology and cardiothoracic surgery teams reviewed prior and repeat echocardiographic studies and a 3 × 1 cm perivalvular echodensity suggestive of a perivalvular abscess was noted in all imaging studies including echocardiography done 1 month prior to her current admission. The hospital course of the patient was complicated by development of intermittent headaches. Magnetic resonance imaging of the brain performed on day 10 revealed a subarachnoid haemorrhage and small foci of possible septic emboli. A magnetic resonance angiogram did not show intracranial vascular aneurysms. The coagulation panel at that time was within therapeutic range and therefore it was presumed that neurological manifestations were related to *M. abscessus* endocarditis. The patient was considered high risk for valvular replacement surgery based on the recent intracranial haemorrhage, poor nutritional status and co-morbidities. After multiple discussions with the surgical team, the patient declined valve replacement. The patient was continued on imipenem, amikacin and linezolid at the same doses. Unfortunately, on day 19 of hospital admission, the neurological condition of the patient acutely worsened and she 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, meningitis 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 confounded 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-tuberculosis 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 adenine 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 \( \geq 16 \) 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 imipenem 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 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


