CASE REPORT

A rare case of *Mycobacterium abscessus* subspecies *abscessus* prosthetic valve endocarditis and the clinical importance of inducible *erm*(41) gene testing

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SUMMARY

A 56-year-old man with a history of injection drug use and two prior episodes of native valve infective endocarditis presented with dyspnoea on exertion. Our preliminary work-up revealed bacteraemia with reported growth of '*Mycobacterium abscessus* group' on multiple blood cultures. The patient was later found to have eustachian valve and prosthetic pulmonic valve endocarditis. Initially, he responded to standard antimycobacterial therapy for rapidly growing mycobacteria (RGM) with supporting laboratory susceptibilities. However, he later developed refractory disease and persistent bacteraemia in the setting of these alleged susceptible antibiotics. Further molecular testing revealed a functional and inducible *erm*(41) gene which confers macrolide resistance. A subspecies analysis of the *M abscessus* group revealed the subspecies to be *abscessus*. We present a challenging case of *M abscessus* subsp. *abscessus* bacteraemia and prosthetic valve endocarditis with further discussion on treatment and management of this infection along with the taxonomic complexity of this ubiquitous RGM.

BACKGROUND

Mycobacterium abscessus is a non-tuberculous mycobacteria that was recognised as a distinct species in 1953 when it was isolated from a chronic knee infection.¹ It was further delineated from *Mycobacterium chelonae/abscessus* or *Mycobacterium fortuitum/chelonae* complexes through 16S rRNA gene sequencing in 1992.² These mycobacterium usually demonstrate rapid growth in vitro and have been termed the rapidly growing mycobacteria (RGM).^{2,3} After *M abscessus* was considered its own species, new molecular techniques have now identified a group of three separate subspecies which include *M abscessus* subsp. *abscessus*, *M abscessus* subsp. *bolletii* and *M abscessus* subsp. *massiliense*.⁴ The importance of *M abscessus* subspecies identification has been debated but recent developments are now indicating that proper identification is an important aspect in managing this RGM infection. *M abscessus* subsp. *abscessus* is well known for drug resistance and has been shown to be refractory to treatment.^{4,5} They are innately macrolide resistant due to the presence of an inducible gene that is phenotypically expressed when exposed to macrolide antibiotics. The erythromycin ribosomal methyltransferase (*erm*) (41) gene stimulates the

expression of a diverse collection of methylases that ultimately lead to impaired binding of macrolides to the 23S ribosomal subunit, thus, preventing their inhibitory mechanism.⁶

CASE PRESENTATION

A transient 56-year-old Caucasian man presented to the emergency department with complaints of dyspnoea on exertion and uncontrollable 'hiccups' of 3 weeks duration. Exercise tolerance was approximately two blocks before having to stop and rest. He denied chest pain, orthopnoea, dizziness, fever, leg swelling or palpitations. Medical history was significant for pulmonary embolism, methicillin-sensitive *Staphylococcus aureus* (MSSA) native pulmonic valve infective endocarditis (IE) in 2012, *Candida albicans* native pulmonic/eustachian valve IE in 2013 (on prophylaxis with fluconazole 600 mg daily), with subsequent pulmonic homograft graft placement in 2013. Social history revealed a transient lifestyle and polysubstance abuse with active intravenous drug abuse (IVDA) with methamphetamine. Patient has been disengaged from immediate family for many years and was unaware of any familial history of disease. Pertinent findings on the physical exam revealed scattered rhonchus breath sounds and prominent decrescendo diastolic murmur in the pulmonic region. The foot exam revealed several non-tender haemorrhagic lesions in the distal toes (figure 1) which are new to the patient. His vital signs revealed he was afebrile with an irregular heart rate 100 bpm; oxygen saturation 98% on 2 L nasal cannula. Initial laboratory findings showed pancytopenia (white blood cell 2.9 1000/ μ L, Hemoglobin 11.8 mg/dL, Platelet 130 1000/ μ L) and creatinine 0.9 mg/dL. Erythrocyte sedimentation rate was 13 mm/hour, C reactive protein 2.65 mg/dL and alkaline phosphatase 534 IU/L. Serum (1,3) beta-D-glucan (biomarker for invasive fungal disease) was obtained due to his history *C albicans* fungemia and fungal IE with the worry he may have recurrence. It resulted as 35 pg/mL (reference intervals: <59 pg/mL/mL: negative, 60–79 pg/mL: indeterminate, $\geq$ 80 pg/mL/mL: positive). CT of the chest with contrast revealed unchanged findings of chronic pulmonary embolism along with new scattered lung nodules measuring up to 5 mm in multiple lobes that were not seen on prior imaging 2 years ago. Patient was admitted to the hospital for further inpatient work-up.

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Figure 1 Distal right great toe with new non-tender haemorrhagic lesion (red arrow) in the setting of bacteraemia likely representing septic emboli (Janeway lesion).

A transoesophageal echocardiogram (TEE) was done with concerns that the prominent pulmonic diastolic murmur and possible septic emboli (distal toe haemorrhagic lesions and new scattered lung nodules on chest imaging) was indeed evidence of IE. The TEE subsequently revealed a new highly mobile pedunculated vegetation on the eustachian valve measuring $0.65\text{ cm} \times 0.71\text{ cm}$ (figure 2) accompanied by another new large mobile vegetation on the prosthetic pulmonic valve (figure 3) protruding into the main pulmonary artery without evidence of paravalvular fluid collection. Patient was started on empiric intravenous vancomycin, piperacillin/tazobactam and fluconazole given his history of prior IE with MSSA and *C albicans* in the setting of active IVDA. Blood cultures from admission

Figure 2 Three-dimensional transoesophageal echocardiogram demonstrating new vegetation (red arrow) on the eustachian valve (venous valve at the junction of inferior vena cava and right atrium).

Figure 3 Pedunculating mass (red circle) located on the prosthetic pulmonic valve as seen on three-dimensional transoesophageal echocardiogram.

soon revealed growth '*M abscessus* group' from three out of three bottles on day 2 as reported from our microbiology laboratory. Cardiothoracic surgery was consulted due to the definite diagnosis of prosthetic valve IE (based on the modified Duke criteria for IE) with supporting evidence being the discovery of new vegetation's seen on TEE, three blood cultures positive with first and last sample being drawn at least 1 hour apart, presence of immunological phenomena and IVDA. In light of the patient's active IVDA history, the cardiothoracic surgeon recommended against surgical intervention at this time and continue with medical management. Patient was then started on intravenous amikacin 7.5 mg/kg every other day, cefoxitin 2g every 6 hours and imipenem/cilastatin 1g every 6 hours. He began to exhibit oliguria and a rising serum creatinine. The likely offending agent to his acute kidney injury was attributed to amikacin but did resolve after this medication was switched to linezolid 600mg daily. He continued this antimycobacterial regimen and repeat blood cultures revealed negative growth. While awaiting antibiotic sensitivities the patient began to clinically improve and he decided to leave the hospital against medical advice. Antibiotic sensitivities which were sent to an outside laboratory came back after 7 days and revealed antibiotic susceptibility to amikacin, tigecycline and clarithromycin with intermediate susceptibility to cefoxitin, imipenem, linezolid and resistance to quinolones, tetracyclines and trimethoprim-sulfamethoxazole (table 1).

The patient returned to the hospital seeking medical attention 3 weeks later with symptoms that were similar to his prior admission. Blood cultures at that time again revealed growth from '*M abscessus* group'. Based on the reported sensitivities from the prior admission, the patient was then placed on intravenous cefoxitin 2g every 12 hours (renally adjusted), oral linezolid 600mg daily and oral clarithromycin 500mg twice daily. The specimens were again sent to the same outside laboratory with reported similar antibiotic susceptibility interpretations from prior admission. Multiple repeated blood cultures were done in the setting of the above antimycobacterial regimen but surprisingly remained positive for >10 days. The patient then began to spike fever and experienced leucocytosis. With persistent '*M abscessus* group' bacteraemia and spiking fever, we decided to

Table 1 Initial '*Mycobacterium abscessus* group' antimycobacterial susceptibilities

Antibiotic	Minimum inhibitory concentration dilution	Interpretation
Amikacin	16	Susceptible
Cefoxitin	32	Intermediate
Ciprofloxacin	≥8	Resistant
Clarithromycin	1	Susceptible
Doxycycline	≥32	Resistant
Imipenem	8	Intermediate
Linezolid	16	Intermediate
Minocycline	≥16	Resistant
Moxifloxacin	≥16	Resistant
Tigecycline	0.25	No interpretation
	≥16/304	Resistant

send a specimen to a centre specialising in identifying RGM. Their analysis revealed the presence of *M abscessus* subsp. *abscessus* through 16S ribosomal typing and DNA genotyping. This RGM was also positive for a functional *erm(41)* gene and subsequent prolonged incubation in the presence of macrolide revealed inducible resistance to clarithromycin.

TREATMENT

Based on the knowledge of a highly resistant *M abscessus* subsp. *abscessus* infection with inducible macrolide resistance, the antimycobacterial regimen was changed to intravenous amikacin 7.5 mg/kg three times weekly (renally dosed), cefoxitin 2g every 8 hours and imipenem-cilastatin 1g every 6 hours. Expected duration of therapy was for 6–12 months as tolerated because the prosthetic valve was unable to be surgically repaired or replaced.

OUTCOME AND FOLLOW-UP

After initiating the proper targeted antimycobacterial therapy, the patient cleared the *M abscessus* subsp. *abscessus* bacteraemia on the first set of repeat blood cultures. He responded well clinically and did not develop any further kidney injury. He was discharged to a skilled-nursing facility for continued management. After completing 6 months of therapy, he had no complaints related to clinical endocarditis and was functionally back to baseline. He did however develop ototoxicity that was observed on serial hearing testing. The patient did not require hearing aid devices to maintain a comfortable ability to hear but was noted to have some permanent hearing impairment. Ototoxicity is a known adverse side effect of aminoglycoside use. We discussed risks and benefits of amikacin use prior to its administration. The patient agreed that amikacin was needed for the optimal treatment of this severe infection given the highly resistant patterns of his *M abscessus* subsp. *abscessus* isolate. Unfortunately at the 1 year mark the patient missed outpatient clinic follow-up. It was discovered that he had recently left the skilled-nursing facility against medical advice and has since been lost to follow-up.

DISCUSSION

This case demonstrates the importance of further *Mycobacterium abscessus* subspecies identification along with prolonged (>14 days) susceptibility testing for inducible and functional *erm(41)* gene expression. In the 1990s, the backbone drug of choice for *M abscessus* complex infections was a macrolide-like

clarithromycin.⁷ When treatment failures began to emerge, a mechanism of this resistance pattern was explored. Macrolide resistance was then soon discovered and described in the *M abscessus* complex. It was termed the *erm(41)* gene and when functional would confer resistance to all macrolide antibiotics.^{5–7} The *erm(41)* gene encodes for proteins that methylate ribosomal DNA in the 23S region of the 50S ribosome. The methylation causes a conformational change that prevents macrolides from binding which explains the mechanism of resistance.⁷ Each subspecies of *M abscessus* has their own unique *erm(41)* gene sequence which can be identified via molecular targeting.⁵ *M abscessus* subsp. *abscessus* and *M abscessus* subsp. *bolletii* contain a functional *erm(41)* gene that will yield inducible resistance to macrolides when exposed. On the contrary, *M abscessus* subsp. *massiliense* contains a large deletion in the *erm(41)* gene which renders a non-functional gene.⁶ In the setting of no prior exposure to macrolides, *M abscessus* subsp. *massiliense* will yield both in vitro and in vivo macrolide susceptibility.⁵ As with our case, most laboratories are not equipped to further identify *M abscessus* into its proper subspecies and will simply report the RGM as *M abscessus* 'group' or 'complex'. At this point it is important that these samples are then sent to a laboratory that is familiar with *M abscessus* subspecies analysis and inducible *erm(41)* gene expression. Initially *M abscessus* subsp. *abscessus* will demonstrate macrolide susceptibility in vitro. However, without prolonged incubation periods (>14 days) in the presence of macrolide the microbiologist will not know an inducible *erm(41)* gene is present and in vitro macrolide resistance will not be noted.^{5–7} This was evident in our case after the patient continued to be bacteraemic until subspecies analysis was done and macrolide resistance was discovered. It was not until the antimycobacterial treatment was changed and clarithromycin was discontinued that the patient showed clinical signs of improvement and negative growth on blood culture.

When RGM are identified in bacteraemic patients, a general recommendation is to initiate empiric treatment with amikacin, a quinolone and a macrolide.⁸ Clinicians should be guarded with using a macrolide as an empiric therapy when *M abscessus* 'group' or 'complex' is reported on blood culture without proper subspecies analysis. Knowing that innate resistance patterns are expressed by *M abscessus* subsp. *abscessus*, clinicians should take all the necessary actions to confirm that a functional *erm(41)* gene is not present as well and proper prolonged incubation is done to test for inducible macrolide resistance. Combination therapy of at least two antimycobacterial agents is recommended but usually three separate agents from different classes are used. A minimum duration of 4 weeks is documented in the literature but longer periods consisting of 6–12 months are more common. Removal of any intravascular or intracardiac device is generally strongly recommended and outcomes have shown to be superior after removal.⁸ Unfortunately our patient had a proven history of uncontrolled intravenous drug use, thus, surgical intervention was not done in fear of possible reinfection.

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Learning points

- ▶ Rapidly growing mycobacteria are a diverse group of non-tubercular mycobacteria and should be subspeciated, so appropriate therapy can be implemented.
- ▶ *Mycobacterium abscessus* contains a group of subspecies which include *M abscessus* subsp. *abscessus*, *M abscessus* subsp. *bolletii* and *M abscessus* subsp. *massiliense*.
- ▶ *M abscessus* subsp. *abscessus* and *M abscessus* subsp. *bolletii* can harbour a functional *erm(41)* gene which will lead to inducible macrolide resistance.
- ▶ A prolonged incubation period (>14 days) in the presence of macrolide should be done to test for inducible *erm(41)* expression and in vitro resistance to macrolides.

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