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Literature Review

Mycobacterium Abscessus Native Tricuspid Valve Endocarditis. Is a Six-Week Course of Combination Antibiotic Therapy Enough?

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Abstract: A 24-year-old Caucasian woman with a history of intravenous drug abuse and multiple hospital admissions for substance abuse related medical problems presented with pneumonia and was discharged home on oral antibiotics. Three days later, her blood culture grew acid fast bacilli, which was subsequently identified as *M. abscessus* subspecies *abscessus*. Transthoracic and transesophageal echocardiogram (TTE and TEE respectively) was suggestive of tricuspid valve (TV) endocarditis. CT scan of the chest showed evidence of septic pulmonary emboli, pneumonic consolidation and pleural effusion requiring chest tube placement. BAL and blood cultures grew *Mycobacterium abscessus* while pleural fluid cultures remained sterile. She was treated with a combination antibiotic therapy and completed a six-week course with resolution of her symptoms and microbiological cure. We present this rare case of *M. abscessus* native tricuspid valve endocarditis associated with lung infection treated with a short course of combination antibiotic therapy.

Keywords: *Mycobacterium abscessus*, Endocarditis, Intravenous Drug Use, Combination Antibiotic Therapy

Introduction

Mycobacterium abscessus is a nontuberculous acid-fast bacillus commonly found in water, soil, or dust. It is categorized as a rapidly growing mycobacterium (RGM) and is considered difficult to treat due to different mechanisms of antibiotic resistance (Huth *et al*., 2015; Mishra *et al*., 2015). It is commonly acquired through unsterile injections, invasive medical procedures that used contaminated equipment, or contaminated soil that enters an open wound (CDC, 2010). *M. abscessus* most commonly infects the skin and soft tissues or lungs. Although mycobacterial endocarditis is rare, it should be considered in a differential diagnosis when evaluating a septic patient with prosthetic cardiac devices, trauma, indwelling vascular access, a history of intravenous drug use, recent surgical procedures, or immunocompromised status (Huth *et al*., 2015; Bush *et al*., 2011; Rodge *et al*., 2017). Approximately 5-10% of all IE cases are right-sided endocarditis. Of those, about 90% involve the tricuspid valve (TV) and septic pulmonary emboli occur in about 5.7% of the patients (Song *et al*., 2016). TV endocarditis is strongly associated with intravenous drug use (Rodge *et al*., 2017). Infective endocarditis (IE) of the native heart valves due to *M abscessus* has been reported in persons who inject drugs (PWID) and in persons with central venous catheters (Hussain *et al*., 2017; Liebeskind *et al*., 2001). Only one case thus far has been reported with survival beyond 4 months of completion of antibiotic therapy (Huth *et al*., 2015).

Case Report

A 24-year-old Caucasian women with a history of intravenous drug use and multiple prior admissions to our hospital presented to the emergency department with intermittent fevers for 3-4 months. She was having chills, night sweats and productive cough without hemoptysis for the past 3 days. She acknowledged using cocaine and intravenous heroin every few days after being discharged from our hospital six months ago at which time she was treated with a 6 weeks course of intravenous antibiotics for methicillin resistant *Staphylococcus aureus* endocarditis (MRSA) of the tricuspid valve associated with septic pulmonary emboli. She also had a MRSA abscess in the right upper arm that required incision and drainage.

She was afebrile on presentation and had multiple track marks in her upper extremities. Chest examination demonstrated decreased breath sounds in the right infra-scapular area with some crackles. Her white blood cell count (WBC) was 6900/μL, hemoglobin was 10.9 gm/dL and platelets were 209,000/μL. Her creatinine was 1.86 mg/dL with an estimated GFR of 33 ml/min. Human immunodeficiency virus (HIV) antigen and antibody test was negative. Chest radiograph demonstrated right lower lobe airspace disease suggestive of pneumonia. Patient was admitted for IV antibiotic therapy and hydration and received 3 days of IV ceftaroline. She remained afebrile and was discharged home on trimethoprim/sulfamethoxazole (TMP/SMX) and amoxicillin/clavulanate for presumed community acquired pneumonia. After she was discharged, growth of acid-fast bacilli (AFB) was reported from each aerobic bottle of 2 sets drawn on hospital day 1 and 2. A rapidly growing mycobacterial (RGM) infection was suspected and she was called to be admitted to the hospital. She was empirically treated with azithromycin, amikacin and imipenem. A transthoracic echocardiogram (TTE) demonstrated a freely mobile 7×7 mm echodensity attached to the TV associated with mild tricuspid regurgitation directed towards the interatrial septum (Fig. 1). CT angiogram of the chest showed filling defects within several large right lower lobe pulmonary arteries, dense right lower lobe consolidation with trace pleural effusion and mediastinal and right hilar adenopathy (Fig. 2). The transesophageal echocardiogram demonstrated 15 mm vegetation in the TV with moderate tricuspid regurgitation. A CT chest performed 5 days after admission, due to worsening shortness of breath, showed progressive consolidative changes in the right lower lobe along with new consolidation in the right middle lobe and increasing mild to moderate right pleural effusion. Cardiothoracic surgical team was consulted for surgical recommendation.

The patient underwent bronchoscopy with bronchoalveolar lavage (BAL) and therapeutic thoracoscopy with drainage and thoracostomy tube placement on day 8 of hospitalization. Sero-sanguineous fluid was noted in the tube drain. Chest tube remained in place for 48 hr and was removed without complication. BAL cultures were reported growing AFB as well. At this point, linezolid was added to the regimen. Multiple sets of blood cultures drawn during the hospital course were negative after starting combination antibiotic therapy. Pleural fluid AFB cultures remained negative. Drug susceptibilities were available 3 weeks later (performed at University of Texas Health Science Center in Tyler, TX). The isolate was reported susceptible to amikacin. Linezolid, imipenem and cefoxitin were reported to have intermediate activity and TMP/SMX, ciprofloxacin, moxifloxacin, doxycycline, minocycline and clarithromycin were reported resistant (Table 1).

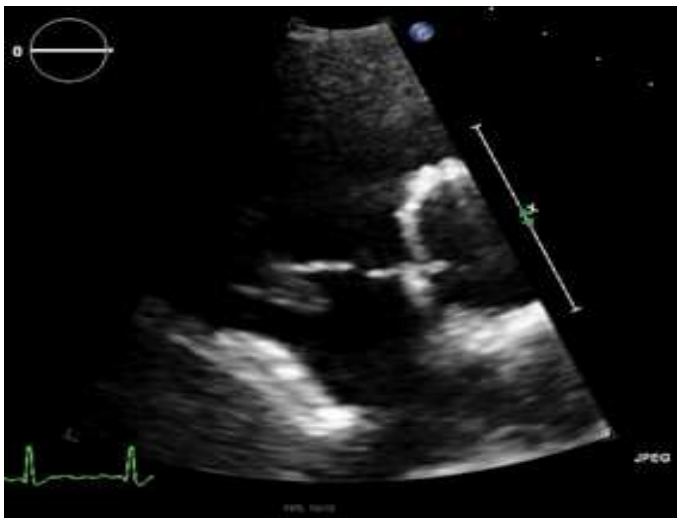

Fig. 1: Transthoracic echocardiogram ejection fraction = 60-65%. There is trace mitral regurgitation. There is mild tricuspid regurgitation. Mobile echodensity on the tricuspid valve consistent with vegetation, measuring 1.5 cm

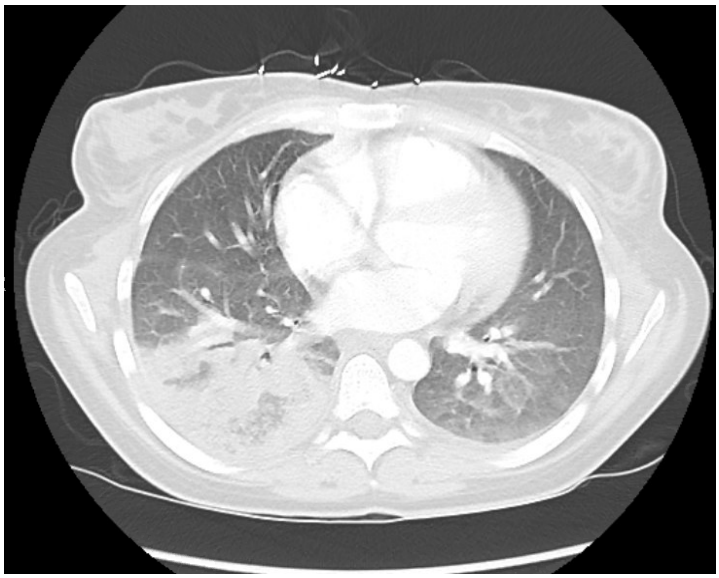

Fig. 2: 1st CTA Chest (Day 3) Low-density central filling defects within several right lower lobe pulmonary arteries consistent with persistent or recurrent pulmonary embolic disease with concomitant dense consolidation

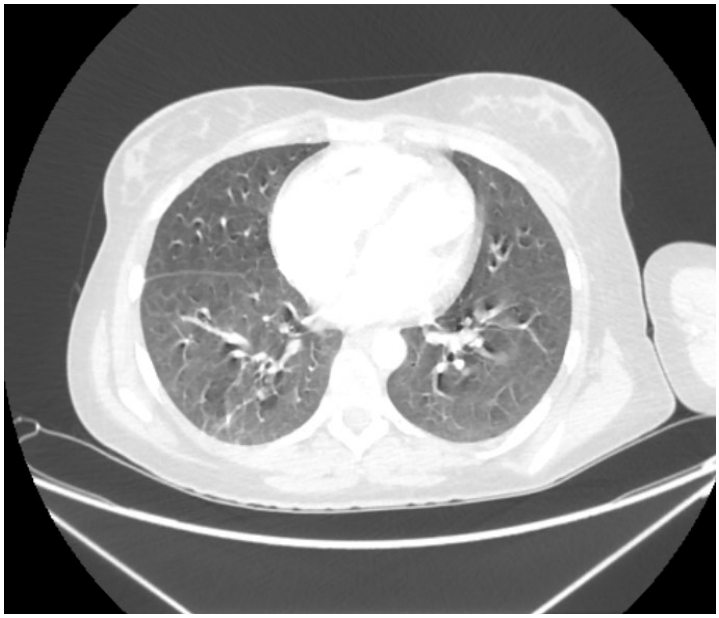

Fig. 3: Follow-up Chest CT Scan (1 year after completion of therapy and thoracostomy tube removal). The trachea and main bronchi are within normal limits. There is no evidence of a pneumothorax or pleural effusion. There is mild bibasilar subsegmental atelectasis. Otherwise, no focal airspace opacities are identified.

Inducible erm gene was noted to be present in the isolate and azithromycin and linezolid were discontinued and tigecycline was added to imipenem and amikacin. The patient continued to do well on combination therapy except for mild nausea requiring ondansetron as needed. The patient completed 6 weeks of antibiotics from the day of first negative blood culture (Table 2). When seen in the clinic 2 weeks after discharge, she had full resolution of her symptoms. A repeat TTE 1 month after completion of therapy demonstrated a decrease in size of tricuspid valve vegetation. Blood culture done 3 months later were sterile. A year later AFB blood cultures were done and remained negative and a repeat CT scan of the chest demonstrated resolution of pneumonia and effusion (Fig. 3).

Table 1: *Mycobacterium abscessus* susceptibilities

Antibiotic	Microdilution MIC (µg/mL)	S	I	R
TMP/SMX	4/76			√
Linezolid	16		√	
Ciprofloxacin	>4			√
Imipenem	8		√	
Moxifloxacin	>8			√
Cefoxitin	32		√	
Amikacin	8	√		
Doxycycline	>16			√
Minocycline	>8			√
Tigecycline	0.06			-
Tobramycin	-			-
Clarithromycin	>16			√
Ertapenem	-			-
Meropenem	-			-
Clofazimine	0.25			

MIC-minimal inhibitory concentration, SMX-sulfamethoxazole,
TMP-trimethoprim. S-susceptible, I-intermediate, R-resistant

Table 2: Antibiotic regimen used in current patient

Antibiotic used	Dose	Duration
Azithromycin	500 mg daily	D1-D16
Amikacin	15 mg/kg daily to start and adjusted afterwards for trough <4 and peak of 50.	D1-D42
Imipenem	500 mg Q6 hr	D1-D42
Linezolid	600 mg Q12 hr	D9-D17
Tigecycline	100 mg once and 50 mg Q12 hr	D17-D42

D = days

Discussion

Bloodstream infections complicated by infective endocarditis due to unusual organisms such as *Candida* species and nontuberculous mycobacteria (NTM) are occasionally encountered in PWID. Disseminated RGM infection have been described in persons with underlying hematologic malignancies on chemotherapy, renal transplantation, autoimmune diseases and defects in interleukin-12 and interferon-gamma pathways (Redelman□Sidi and Sepkowitz, 2010). *M. abscessus* is one of about 20 human pathogen species of RGM and unusual cause of bloodstream infection and endocarditis in immunocompetent patients (El Helou *et al*., 2013). *M. abscessus* is known to produce biofilm and resist common disinfectants (Zambrano and Kolter, 2005). Municipal water supply systems could harbor this bacterium and can cause infection when contaminated water is used for intravenous injection (Zhang *et al*., 1997). We presume IV injection as the portal of entry in our case as the patient used tap water as a diluent.

Native valve endocarditis due to *M. abscessus* is rare. PubMed search using "*M abscessus* endocarditis" revealed only a few cases of *M abscessus* native valve endocarditis (Table 3), although several cases of bacteremia, prosthetic valve endocarditis and invasive infections associated with hospital outbreaks have been reported (Redelman□Sidi and Sepkowitz, 2010; El Helou *et al*., 2013; Baker *et al*., 2007; Richey *et al*., 2013; Tsai *et al*., 2008). Use of IV drugs as a risk factor of *M abscessus* endocarditis was documented by (Tsai *et al*. 2008; Garcia *et al*., 2014) and Huth *et al*. (2015). The presence of central or peripherally inserted catheters, hemodialysis catheters and coronary angiogram have also been described as the predisposing factors by others (Rodge *et al*., 2017; Williamson *et al*., 2009; Al-Benwan *et al*., 2010). Tricuspid and mitral valve involvement have been reported more often than the aortic valve. Although a male to female ratio of 1.38:1 of mycobacterial endocarditis was described by (Yuan, 2015), we found a male to female ratio of 3.5: 1 for native valve endocarditis due to *M abscessus*.

Diagnosis of *M abscessus* blood stream infection can usually be made from routine blood cultures in 3-4 days. A broth microdilution method is recommended for antimicrobial susceptibility testing by the National Committee for Clinical Laboratory Standards. MALDI-TOF MS is suggested to discriminate *M. abscessus* subspecies *bolletii, abscessus* and *massiliense* (Fangous *et al*., 2014). Macrolide resistance is rarely demonstrable at day 3 of incubation for this species. A minimum inhibitory concentration (MIC) read is recommended to be performed on day 14 of incubation and Erythromycin Ribosome Methyltransferase (ERM) gene sequencing can be done to detect an inducible erm gene. In our case, erm gene sequencing was performed at UTHSCT and revealed a functional erm gene indicating resistance to macrolides. We modified our antibiotic

regimen accordingly. Erythromycin ribosome methyltransferase (ERM), aminoglycoside acetyltransferases, an aminoglycoside phosphotransferase, a rifamycin ADP-ribosyltransferase, a β-lactamase and a monooxygenase have been identified as responsible mechanisms for resistance of *M. abscessus* to different classes of antibiotics (Sfeir *et al*., 2018). Antimicrobial susceptibility testing of *M abscessus* reported from Taiwan revealed susceptibility rate of 100% with tigecycline, 95% with amikacin, 92.5% with clarithromycin, 32.5% with cefoxitin, 22.5% with moxifloxacin, 12.5% with imipenem, 10% with ciprofloxacin, 7.5% with doxycycline and 7.5% with sulfamethoxazole (Huang *et al*., 2010). A recent report from the US showed similar susceptibility patterns with amikacin (93.8%), clarithromycin (93.8%), tigecycline (89.1%), linezolid (44%) and doxycycline (12%) (Fangous *et al*., 2014). Imipenem MICs are not usually reported for *M. abscessus* due to lack of reproducibility (Brown-Elliott and Wallace, 2002). It may be appropriate to consider MICs and concentration rather than susceptible and resistant in selecting a drug. A drug with very high MICs *in vitro* is unlikely to be active *in vivo* whereas one just above a 'critical concentration' may have some activity, when combined with additive or synergistic agents (Haworth *et al*., 2017).

Table 3: Cases of *M abscessus* native valve endocarditis

Author, Year of publication	Patient's Age (years)/Sex, Country of reporting	Predisposing factors/ Association described	Valve involved	Culture source/ Confirmation	Surgery or Antimicrobial therapy	Outcome
Liebeskind *et al*. (2001)	35/M, USA	Trip to El Salvador	Mitral	Blood, bone marrow and CSF. Autopsy evidence of endocarditis.	IV ciprofloxacin, meropenem and amikacin later switched to clarithromycin and imipenem. No surgery.	Expired on day 69.
Corrales-Medina *et al*. (2006)	43/M, USA	Construction worker, colostomy	Aortic	Blood, valve culture	Imipenem, linezolid and clarithromycin→ AVR on day 50 → clarithromycin and imipenem → clarithromycin, meropenem and amikacin.	Expired on day 160.
Tsai *et al*. (2008)	29/M, Taiwan	IV heroin user	Tricuspid	Blood, sputum	Multiple antibiotics from June 2006- end. No surgery.	Lost to follow up.
Al-Benwan *et al.*, (2010)	54/M, Kuwait	Hemodialysis, Chronic hepatitis C, Perm catheter	Mitral	Blood, perm catheter tip	Clarithromycin and tigecycline → clarithromycin held and tigecycline monotherapy used, non-compliant patient. No surgery.	Expired after 5 weeks of hospitalization.
Williamson *et al.* (2009)	29/F, USA	Hemodialysis, subclavian HD catheter	Mitral	Blood, subclavian catheter culture	Vancomycin → After day 10, HD catheter→ removed vancomycin, piperacillin/ tazobactam and gentamicin→ after day 20 imipenem, moxifloxacin and clarithromycin initiated (when AFB stain demonstrated AFB). No surgery.	Expired after 24 days of *M abscessus* therapy.
Garcia *et al.* (2014)	48/M, USA	IVDA	Mitral	Blood, valve. Coinfection with Kocuria	Vancomycin, ceftriaxone, gentamicin → imipenem, amikacin and azithromycin. MVR done.	Expired 4 months after completion of therapy due to sepsis of unclear etiology.
Huth *et al*. (2015)	52/M, USA	Intravenous drug use	Tricuspid	Blood Note: valve culture negative. Valve tissue: AFB stain positive	Cefoxitin, amikacin, clarithromycin and moxifloxacin → tigecycline, linezolid, clarithromycin and amikacin → day 19 linezolid discontinued, added imipenem. Tricuspid valvectomy on day 41. Tigecycline, amikacin, imipenem and clarithromycin continued till day 77 when amikacin was discontinued. Antibiotics discontinued 2 months after valve surgery.	Cure.
Mishra *et al*. (2015)	53/M, India	Coronary angiogram	Aortic	Blood	Five different antibiotics administered. No surgery.	Expired.
Rodge *et al*. (2017)	61/F, India	PICC, chemotherapy, Non-Hodgkin's lymphoma	Tricuspid	Blood, valve	IV amikacin, linezolid, moxifloxacin and clarithromycin. TVR done.	Expired.

AFB = acid fast bacilli, TVR = tricuspid valve replacement, PICC = peripherally inserted central catheter, MVR: mitral valve replacement

Treatment regimens for *M. Abscessus* endocarditis is not clear due to lack of randomized controlled trials. The regimens used in the past have varied, but most have used three or more antibiotics. (El Helou *et al*., 2013) suggested the use at least 2 active antimicrobial agents to treat *M abscessus* bacteremia (El Helou *et al*., 2013). A minimum of 4 months of combination antibiotic therapy is recommended for treatment of serious infection due to *M abscessus* (Griffith *et al*., 2007). We used three agents throughout the course of six weeks. Previous reports that demonstrated cure of *M. abscessus* endocarditis mention use of more than three different antibiotics (Huth *et al*., 2015) along with surgical intervention. In our patient, we wanted patient to receive a few more days of antibiotics before undergoing valve surgery as we feared bacterial seeding in a new valve. However, she improved clinically and decision was made not to perform surgery. Haworth *et al*. (2017) recommended at least 4 weeks of combination antibiotic therapy for treatment of pulmonary *M abscessus* infection and suggested to consider duration of intravenous treatment based on the severity of infection, treatment response and tolerance of the regimen.

Although there is no consensus in terms of combination therapy, we suggest considering 3 or more agents, if tolerated, to eradicate the infection. Due to lack of data, we are unable to recommend a short course of antibiotic therapy. Due to the challenges associated with timely diagnosis, treatment and substance abuse management, these patients often pose an economic burden to our healthcare system. This case opens a debate, if in a selected group of patients, a short course of combination antibiotic therapy is enough to obtain cure. This would need further analysis.

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Author's Contributions

Rabindra Ghimire: Treated the patient, collected and analyzed the data, wrote the draft and revised the final draft of the manuscript.

Dora Lebron: Treated the patient, wrote the first draft and reviewed the final manuscript.

William Matthew Wooten: Submitted the abstract form in the ID week 2019 and reviewed the final manuscript.

Niki Tyler Winters: Wrote the first draft, collected imaging findings, and reviewed the final manuscript.

John M Cahill: Reviewed the imaging findings, treated patient and reviewed the final manuscript.

Alicia Lagasca, Alexandra Stang and Paul Cook: treated the patient and reviewed the final manuscript.

All authors have read and approved the contents of this manuscript.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

Disclosures

Authors declare that the abstract of this case was presented as a poster presentation in ID Week 2019 and had received a travel grant from IDSA. There is no other financial disclosure to be made.

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