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Case Report

Cure of Polymicrobial Mycobacterium Abscessus and Chelonae Endocarditis Through Integrated Medical and Addiction Treatment

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Abstract

We present here a case of tricuspid valve endocarditis in a person who injects drugs (PWID) with *Mycobacterium chelonae* and *Mycobacterium abscessus* successfully treated with a combined medical and surgical approach. This case highlights multiple challenges faced in the cases of treating injection drug use endocarditis including delays in identification and diagnosis of mycobacterial organisms, concern for intravenous line manipulation, poly microbial endocarditis which can be difficult to detect, and need for patients to be admitted for prolonged periods. A systematic literature review of M. abscessus endocarditis is provided with parallels and teaching points between our case and the 14 additional reported cases identified, particularly our approach to addiction treatment in order to facilitate cure in this patient.

Keywords: Endocarditis, Mycobacterium, Injection Drug Use, Integrated Care

Introduction

Endocarditis, the infection of heart valves, has increased more than 12-fold amidst the opioid epidemic [1]. This condition has high morbidity and mortality even when caused by classic pathogens. People who inject drugs (PWID) are at risk for atypical pathogens including mycobacteria with high mortality. Treatment is complex and frequently fails in part due to difficulty in retaining a PWID in care with the need for prolonged intravenous antibiotics. We present here details of a successful outcome and review of the literature with emphasis on treatment of both the infection and the substance use disorder.

Case Report

A 39-year-old male presented to his local hospital with a 2-day history of dyspnea, cough and subjective fever. He had no significant past medical history except for chronic back pain and injection drug. Blood cultures grew viridans streptococci and intravenous (IV) ceftriaxone 2 grams daily was started. A transthoracic echocardiogram (TTE) performed on day 2 (D2) showed two small vegetations on the tricuspid valve (TV) associated with severe regurgitation. He underwent valve replacement with a bio prosthetic valve on D40. Four days later (D44) he developed rigors and malaise and blood cultures grew *Candida albicans*. Treatment with IV ceftriaxone for 6 weeks was completed but he had been started on micafungin with candida investigations ongoing when the patient left against medical advice (D49) before after he was found with syringes with pink residue in his possession and strong suspicion that he was continuing to inject drugs and manipulate his IV line.

The patient presented 4 days later (D53) to Wake Forest Baptist Hospital (WFBH). Contact with the OSH revealed that an acid fast bacillus (AFB) had grown from those same blood cultures which grew the *C. albicans*. It had been sent to a reference laboratory for identification. Transesophageal Echocardiogram (TEE) revealed a healthy appearing prosthetic valve and ophthalmic exam was benign with no candida grown on cultures here. Given that he was clinically stable, and it was not clear when further information on

the AFB would be available, he was discharged home with a 14-day course of fluconazole 400 mg PO daily close outpatient follow-up.

He was re-admitted about 3 weeks later (D79) when another blood culture was positive for AFB which was confirmed to be *M. abscessus* by WFBH laboratories and sent to a separate reference laboratory for antimicrobial susceptibility testing. Repeat TEE on WFBH hospital day 7 (WFBH7/D86) showed a mobile echodensity of the TV suspicious for vegetation. Given the belief that the *Mycobacterium* and *Candida* had resulted from ongoing line manipulation and ongoing drug use immediately following his last surgery, he was not considered a candidate for surgery. He was subsequently started (D89) on clarithromycin 500 mg BID, cefoxitin 2 g/4xDaily, amikacin 15 mg/kg/day, and IV imipenem.

More information from the outside hospital became available at this point: the surgical valve tissue culture from the OSH had also grown a *Mycobacterium* 15 days after its collection. On WFBH15/D94 AFB species from the OSH were confirmed through sequencing to be *Mycobacterium chelonae* from the valve tissue and *Mycobacterium abscessus* from the blood. Antimicrobial susceptibility testing on the isolates recovered at the OSH showed the *M. abscessus* as sensitive only to amikacin, intermediate to linezolid, imipenem, and cefoxitin, and resistant to all else including clarithromycin. *M. chelonae* was sensitive to linezolid, clarithromycin and tobramycin but resistant to moxifloxacin, cefoxitin, and imipenem.

One week later (~D100) antimicrobial susceptibility results from the isolate collected at Wake Forest (our hospital) returned and showed a *M. abscessus* which was far more sensitive including sensitive to amikacin, clarithromycin, cefoxitin, linezolid, and tigecycline, intermediate to imipenem and resistant to tetracyclines and moxifloxacin. Cefoxitin was discontinued and linezolid added. On week 10 (~D149), amikacin was discontinued due to hearing loss and was replaced with tigecycline which was discontinued a week later (~D156) for refractory nausea and vomiting. Oral doxycycline 100 mgs BID was started in its place.

All blood cultures during this stay were negative. Despite this, a repeat TTE WFBH94/D153 showed a growing vegetation now measuring 1.0 x 0.9 cm. He then underwent a repeat replacement with a bioprosthetic valve on WFBH100/D159. The valve was found to be grossly deformed with massive vegetations (Figure 1). Valve cultures grew *Candida albicans* and methicillin-susceptible *Staphylococcus aureus* (MSSA). The patient completed an additional 6-week course of micafungin 150 mgs daily, cefazolin 2 gram TID, and clarithromycin, imipenem, doxycycline and linezolid at their current doses. Upon completing this regimen he was transitioned to oral fluconazole 400 mg to be continued indefinitely. He continues to follow up outpatient and remains culture negative and doing well at his most recent visit 1 year post discharge.

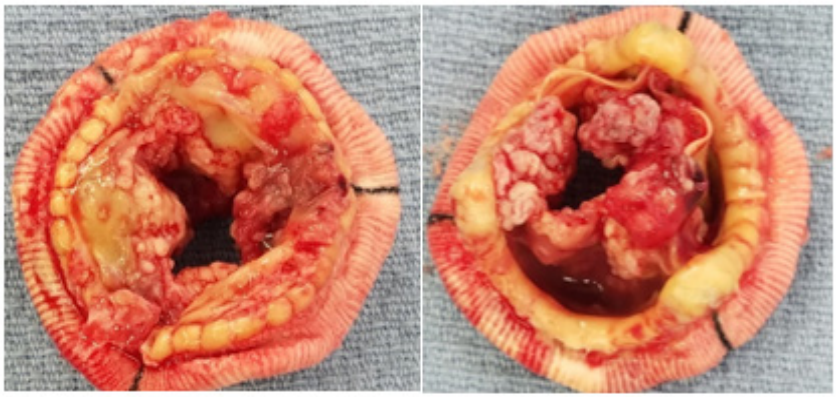

Figure 1: The atrial (left) and ventricular (right) view of the bioprosthetic valve removed on day 159 shows gross malformation with large vegetations.

Discussion and Literature Review

There are multiple salient points to this case. We will start with a discussion of mycobacterial endocarditis. *Mycobacterium abscessus*, *chelonae*, and *fortuitum* are environmental organisms that have been found to cause a myriad of diseases in immunocompetent and immunocompromised hosts. These 3 organisms are designated the rapid growing mycobacteria (RGM) due to their growth within 7 days on culture medium [2]. Identification of RGM is difficult and many laboratories are capable of reporting only M. chelonae/abscessus complex rather than distinguishing the exact species [3]. This distinction is important as the 2 organisms have varying antimicrobial susceptibility patterns and prognoses.

M. abscessus is particularly challenging due to limited treatment options. Of the 3 subspecies of *M. abscessus*, both *abscessus* and *bolletii* frequently have an inducible macrolide resistance (erm) gene [4]. This can result in initial appearance of susceptibility to macrolides with resistance developing after days of therapy; repeat susceptibility testing during treatment is recommended. The drugs clarithromycin, amikacin, and cefoxitin are most commonly determined to be susceptible *in vitro* [5]. However in the case of pulmonary disease, *in vitro* susceptibility fails to predict clinical treatment success. Surgical intervention is encouraged whenever possible to

increase potential for cure [5]. *M. chelonae* lacks the erm resistance gene and is more comparable to other mycobacterial infections with a slightly better outlook than abscessus [5].

A systematic review of all mycobacterial endocarditis from 2000-2013 suggests that 50% of patients will have death or recurrence [6]. This overall poor response is likely exacerbated by delayed and missed diagnoses. Even the rapid growers require 7 days to grow with longer for full identification; in the meantime patients may appear deceptively well with fever curves correlating poorly with disease severity [6]. These organisms are also likely missed in some instances. In a report of 370 valves replaced for culture negative endocarditis, 16s rDNA polymerase chain reaction identified 6 cases of nontuberculous mycobacterial disease (1.6% of cases) [7].

Only 14 cases of *M. abscessus* endocarditis are described in the literature (Table 1). Pubmed was queried using the search terms 'mycobacterium abscessus endocarditis' and '"Endocarditis"[Mesh]) AND "Mycobacterium abscessus"[Mesh]' with 12 citations identified; 2 were excluded as irrelevant and 2 more were found through review of the article references for a total of 13 citations describing 14 cases. Many of these cases developed in immunocompetent hosts and occur with near equal frequency on prosthetic and native valves. The presentation for most patients was indolent and due to inherent delays in diagnosing this organism, many were treated for another condition such as routine bacterial endocarditis or tuberculosis before the definitive diagnosis was made. In at least 2 cases the organism was initially identified as a gram positive rod similar to a *Corynebacterium* spp. The illness typically plays out over the course of months rather than weeks and many cases describe a falsely reassuring course bacteremia persisting despite dissipation of fever and vegetations with active infection persisting despite clearance of blood cultures. Only 1 case apart from our own reported disease cure and surgical intervention was require in that case. The lack AFB growth on our surgical culture suggests our patient had a medical cure though it is possible the antibiotics given in the pre-operative period may have suppressed growth on culture even if the organism was not fully eradicated.

Case	Age	Valve	Presentation	Course	Outcome
Altmann G, et al. [25]	45 yo Immunocompetent Post-surgical Male	Prosthetic AV	Dyspnea, fever, progressive heart failure, signs of aortic insufficiency which progressed despite ampicillin	1) AV is replaced with GPCs on culture initially improves; 2) Readmitted 3 months post-op with pulsating mass on right of sternum; 3) Mycobacteria grow on blood cultures; Biochemically suspect M. chelonae spp abscessus later; confirmed by outside lab; 4) Declines despite PCN, STREP, LINC, and CLOX; 5) Autopsy finds aortic aneurysmal dilation distal to prosthetic AV; multiple vegetations of AV; necrosis and hemorrhage of right atrial wall with AFB throughout aorta	Death at 4.5 months
Repath F, et al. [26]	43 yo Immunocompetent Post-surgical Male	Prosthetic AVProsthetic MV	Had both valves replaced and 4 months later presents with 2 weeks of fever and heart failure	1) Started empirically on PCN and STREP with ongoing fever; 2) At day 4 cultures grow but takes another week for all tests; 3) Day 12 petechial rash and delirium; CSF benign; bone marrow day 14; 4) Hospital and CDC suspect M fortuitum; patient dies despite KAN, ERY, GENT, PCN; 5) Further testing suggests it is not M fortuitum and National Jewish confirms M. chelonae spp abscessus; 6) Autopsy shows lesions both AV/MV; bone marrow AFB positive	Death at day 28
Viscidi R, et DS, et al. al. [27]	55 yo Immunocompetent Post-surgical Male	Prosthetic MV	Patient with 2 prior valve replacements for rheumatic heart disease develops fever and heart failure 4 months after last valve replacement	1) Empiric VANC, GENT given for endocarditis; 2) Anaerobic diphtheroid grows from blood 1 week later; found subsequently to be acid-fast and then identified as M. Chelonae; 3) VANC, ERY started and given 12 days then RIF, INH, ETH and ERY for another week; not a surgical candidate; 4) Sensitivities return and changed to AMI, ETHD and ERY; 5) 10 days after starting this regimen cultures and fever clear; 6) Day 50 sudden decompensation and death	Death at day 50
Wallace RJ, eta la. [28]	Unknown	2 patients with Prosthetic Valves	Not described	Review of 125 rapid growing mycobacterial cases including 4 endocarditis cases all of whom had prosthetic valves. 2 Cases were due to M. abscessus. Both underwent surgical intervention. Exact timings of treatments not stated. All endocarditis patients died.	Death
Libebskind DS, et al. [29]	35 yo Immunocompetent Male	Native MV	5 months fever, weight loss, night sweats, fatigue, altered mentation	1) AFB grows from blood; start CIP, CLA; stroke progression; 2) Start CIP, AMI, MERO; 3) MV replacement deferred; 4) M abscessus grows from CSF drawn on admission; day18 sensitivities return showing R to CIP and MERO; 5) Start IMI, CLA, AMI; 6) Positive bone marrow cultures, progressive seizures, brain herniation	Death Day 69
Corrales-Medina V, et al. [30]	43 yo Immunocompetent Male	Native AV	5 month history of fever, night sweats, 40 pound weight loss and diarrhea	1) M abscessus grows with R to TETs, FQ, RIF but S to TOB, IMI, CEF, AMI, CLA; start IMI, LZD, CLA; 2) Repeat TEE shows bigger vegetation; 3) Valve replacement day 50 with stain and culture AFB positive; 4) After 'surgical recovery period' is discharged on CLA + LZD; 5) Returns 2 weeks later with fever and positive abscessus blood cultures now R to TOB, IMI, CEF, CLA and intermediate to AMI; 6) Start CLA, IMI (switched later to MERO due to seizures) and AMI	Death Day 160

Tsai WC, et al. [31]	29 yo IVDU Male	Native TV	Was treatment for MSSA TV endocarditis medically but developed fever and worsened echo 6 months later	1) Started on RIPE based on AFB smear positive culture; vegetation enlarges though afebrile; 2) 2 months in has fever relapse; species identified as abscessus; CLA, IMI given for 4 weeks with vegetation decreasing in size; 3) Transition to CLA, MOXI at home for about another 3 months then admitted with fever and new vegetation; 4) Restarted on RIF, ETH, INH, CLA; 5) Species identified and changed to CLA, AMI 2 weeks; 6) Changed to oral CLA, CIP administered in clinic 2 months; vegetations smaller but still present	Lost to follow-up at 8 months
Williamson JC, et al. [32]	29 yo Immunocompromised Female	Native MV	Renal transplant performed in India one month prior to admission then presented with 3 weeks of fatigue and weakness	1) Blood cultures grow non-hemolytic colonies with pleomorphic gram positive rod gram stain identified as Corynebacterium with 68% confidence; susceptibility testing through e-test; 2) Vancomycin started; cultures remain positive and P/T + GENT added; 3) Day20 organism grows on fungal blood cultures same as bacterial culture colonies and AFB stain performed; then identified as abscessus; 4) IMI, CLA, MOXI started and cultures clear; 5) Returns susceptible to AMI, CLA, TIG and intermediate to CEF; 6) Pneumonia and fungemia develop	Death ~Day 44
Al-Benwan K, et al. [33]	54 yo Immunocompromised Male	Native MV Native AV	4 weeks of progressive weakness, fever, and weight loss	1) Diagnosed as M abscessus in first week; S to AMI, CLA, IMI, TIG; 2) CLA, TIG for 2 days then refuses CLA due to abdominal pain; TIG alone; fever resolves but cultures stay positive; leaves AMA after 2 weeks; 3) 3 months later presents with same M abscessus and vegetation; 4) CLA and TIG restarted but he is noncompliant and vegetation enlarges; 5) Dies of cardiac arrest 5 weeks after second admission	Death at 9 months
Garcia DC, et al. [34]	48 yo IVDU Male	Native MV	2 months of night sweats, weight loss and dyspnea with 1 week of fever, and abdominal pain	1) E faecalis treated with AMP, GENT and MV replaced with prosthetic valve; valve culture and postsurgical blood cultures grow Kocuria species and M abscessus; 2) IMI, AMI, CLA started; repeat surgery delayed due to shock; organism returns sensitive only to AMI and CLA so IMI stopped; 3) Cultures remain positive so IMI restarted; 4) Cultures clear and he stays inpatient 6 months; 5) Does not follow-up; 6) Re-admitted 4 months later with sepsis and dies in <48 hours; cultures positive for M abscessus	Death at 10 months
Mahajan S, et al. [35]	53 yo Immunocompetent Male	Native AV	Fever develops three weeks after cardiac angiography with echo finding vegetation 6 weeks into workup	1) AFB cultures sent post-echo and empiric LZD, CLA started with growth; 2) M abscessus grows with sensitivities back as S to AMI, CLA, LZD, TOB, I to CEF, R to IMI, TETs; 3) Add INH, ETH, and CEF to regimen; defervesces in 1 week; 4) Marrow suppression with LZD so pause and restart at lower dose; afebrile but cultures remain positive; 5) Patient requests discharge home on the 5 antibiotics after 4 weeks; worsening heart failure and death	Death
Huth RG, et al. [36]	52 yo IVDU Male	Native TV	25 pound weight loss, fever, night sweats of unknown duration	1) AFB grows by day3; start AMI, CEF, CLA and MOXI empirically; 2) S to AMI, R to FQs, I to CEF, LZD, IMI so changed to TIG, LZD, CLA, and AMI; cultures clear; 3) Stop LZD day19 and start IMI; 4) Day31 enlarged vegetation on echo; 5) Day77 stop AMI due to hearing loss; completes 8 weeks of antibiotics from date of surgery and cultures remain negative 2 and 8 weeks later day41 valve debridement with leaflets removed/resected; valve AFB stain positive, culture negative;	Cure
Beatty N, et al. [37]	56 yo IVDU Male	Prosthetic PV Eustachian valve	2 previous episodes of pulmonic endocarditis present with 3 weeks of dyspnea and uncontrollable hiccoughs	1) AFB grow in first week; empiric AMI, CEF, IMI started; develops renal failure; 2) LZD replaces AMI; creatining improves; cultures clear; he leaves AMA; isolate returns S to CLA, AMI, TIG, I to IMI, CEF, LZD and R to FQs; 3) Returns 3 weeks later; CEF, CLA,LZD started; cultures remain positive; 4) 16s ribosomal typing and DNA genotype shows erm(41) gene positivity; changed to AMI, CEF, IMI; ototoxicity develops; 5) Discharged to SNF to complete 6 months but he leaves AMA after partial treatment	Lost to follow-up

AFB- acid fast bacillus; AMA- against medical advice; AMI- amikacin; AMP-ampicillin; AV- aortic valve; CLA- clarithromycin; CLOX-cloxacillin; CEF-cefoxitin; CIP-ciprofloxacin; ETH-ethambutol; ERY-erythromycin; ETHD-ethionamide; FQs- fluoroquinolones; GENT-gentamicin; I-intermediate; IMI-imipenem; INH-isoniazid; KAN-kanamycin ; LINC-lincomycin; LZD-linezolid; MERO-meropenem; MV-mitral valve; PCN- penicillin; P/T-piperacillin/tazobactam; PV-pulmonic valve; R-resistant; RIF-rifampin; S-sensitive; SNF-skilled nursing facility; STREP-streptomycin; TETs-tetracyclines; TIG-tigecycline; TOB-tobramycin; VANC-vancomycin

It is worth noting that the nomenclature and diagnosis of these organisms has evolved over time and results in older case reports being difficult to classify. For example the first rapid growing mycobacterial endocarditis case was reported in 1968 but the organism was only able to be classified as a 'Runyon type IV' mycobacterium [8]; the Runyon classification of nontuberculous mycobacteria divides the organisms into 4 groups based on pigment and growth characteristics and was developed in 1959 [9]. Neither this or another Runyon type IV case [10] are included in this review due to lack of clear species confirmation. M. chelonae did not officially

have recognized subspecies of chelonae and abscessus until an international taxonomic consensus study in 1972 [11] and *M. abscessus* did not become its own species distinct from *M. chelonae* until 1992 [11]. It also must be noted that echocardiograms did not come into widespread use until the late 1970s so many cases reported in the literature before this time as disseminated *M. abscessus* may well have suffered from unidentified endocarditis but would not be identified in this review. Finally, this review does not include cases which occurred in outbreak settings which frequently do not identify the subspecies of *M. chelonae* such as the 1970s occurrence of 25 *M. chelonae* infected porcine prosthetic valves which went on to cause severe infection in at least 2 patients [12].

A second key aspect of this case and review is the treatment of PWID. Of the 14 cases reported, 4 (28%) of these cases were in PWID. These patients may be exposed to the organism from the tap water used to dissolve drugs for injection. A negative aspect of our case is exposure of the biases associated with treatment of these patients. When the patient developed his candidemia and MSSA bacteremia 4 days after his surgery it was assumed that he had manipulated his line/reinjected drugs. However, this may well have not been the case: at least one rapid growing mycobacterium was present on the original valve culture. It is possible that surgery would have been considered earlier, and some negative side effects of the mycobacterial drug regimen avoided, if concern for reinfection from intravenous drug use had not been so prominent in this case. On a positive note, however, our patient did not leave against medical advice and continues to attended follow-up appointments. We believe this is in part due to treatment of his opioid use disorder with buprenorphine and peer counseling interventions recently employed at our institution.

Providing addiction interventions for endocarditis in PWID has been slow and difficult [13,14]. Discharging patients to residential rehabilitation facility where patients can have addiction treatment while finishing their 6-weeks of therapy is not an option for most hospitals due to both resource scarcity and the inability of these facilities to accommodate medically complex patients. In those few areas where such a partnership was able to be built, patients have refused to be transferred [15,16]. This has left hospitals to manage these patients on their own. Some facilities such as Boston Medical Center have developed aspirational care pathways such as the Transitional Opioid Program allowing addiction therapy to begin inpatient and transition seamlessly to outpatient care [17]. Their original model utilized their healthcare-associated, outpatient addiction clinic to coordinate with an inpatient practitioner and since 2015 they have been able to staff their own inpatient addiction consult service [18]. Unfortunately, many rural and resource poor areas are unable to replicate that model [19-21]. Many hospitals have no addiction specialists affiliated with them and even consulting psychiatrists, if available, may have a range of experience and comfort with addiction treatments such as medication-assisted therapy.

In areas with limited addiction resources, both inpatient and outpatient, detoxification with supportive measures and then discharge of patients with numbers to call is frequently all that can be managed. Ironically, this detoxification without a clear plan for continuing high quality addiction care is harmful to patients who are then at increased risk for both non-fatal and fatal overdose [22,23]. In addition, the discomfort of withdrawal layered over a particularly stressful time in the patient's life increase the risk that a patient will leave against medical advice [24]. In order to address both of these concerns, buprenorphine has been provided to interested patients at our institution since 2017. This is administered predominantly through our pain consult team (who manages those with both chronic pain and addiction with buprenorphine) and increasingly through our psychiatry consult team. A grant allows some patients to be seen by a peer navigator or counselor but not all can be accommodated; a weekly NA group has also been started for those retained inpatient for weeks at a time.

Even as our inpatient options have slowly increased, transitioning to and sustaining these therapies outpatient remains difficult. Our experience is that many treatment centers do not provide medication-assisted therapy, are unwilling to schedule appointments before the patient is actually discharged, and/or cannot guarantee they can take over/ refill the buprenorphine started inpatient on their first appointment. Methadone clinics are an option for the uninsured but may have wait lines, be far from rural locations, and not be able to safely prescribe the powerful methadone in patients who suffered recent heart and lung infections. This difficulty has led to our infectious disease physicians to directly bridge the care gap for some of these patients as they are able to act simultaneously as the primary care, ID, and addiction physician for these complex patients following their discharge. One-year later, this patient remains in ongoing addiction care on indefinite fluconazole in his ID provider's clinic.

A final learning point of this case is the potential for polymicrobial disease in PWID. This patient likely had at least 2 organisms on his original presentation: viridans streptococci and an RGM. The RGM was not identified prior to surgery, possibly because of the strict growth requirements and length of incubation needed. That neither the MSSA nor the Candida grew on multiple blood cultures thereafter, however, is difficult to interpret and clinically concerning. The MSSA infection may have been partially treated, but the failure to recover the yeast in subsequent cultures is less easily explained. When an endocarditis patient who injects drugs has vegetations increasing in size on appropriate therapy, clinicians should consider the possibility that they have not identified all of the causative organisms.

Acknowledgement

None.

Conflicts of Interest

None.

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