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Disseminated *Mycobacterium chimaera* infection successfully treated with a clofazimine-containing regimen and long-term follow-up after discontinuing treatment

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ABSTRACT

Mycobacterium chimaera is a slow-growing member of the *Mycobacterium avium* complex. It can contaminate tap water and has been detected in water tanks of heater-cooler devices used during open-heart surgery. Herein we report a case of a 67-year-old- male with disseminated *M. chimaera* infection who presented with fevers, significant weight loss and was found to have bacteremia with prosthetic valve endocarditis, chorioretinitis, bone marrow and splenic granulomas two years after an open-heart surgery. He developed multiple drug adverse events over the course of treatment but was successfully treated using a clofazimine containing regimen along with aortic valve replacement. He has remained symptom-free with no signs of recurrence three years after completion of antimicrobials. Clofazimine is an effective alternative that can be used as part of a multi-drug regimen in *M. chimaera* infection when there is resistance to first-line drugs or when adverse drug reactions occur.

Introduction

Mycobacterium chimaera is a slow-growing nontuberculous mycobacterium (NTM) sequevar belonging to the Mycobacterium avium complex (MAC). M. chimaera has emerged as a global public health concern due to infections following cardiac surgery caused by contaminated devices, specifically heater-cooler units (HCU), used to regulate blood temperature during extracorporeal circulation. Managing *M. chimaera* infection proves challenging, with high morbidity and mortality resulting from difficulties in both diagnosis and therapy. Consequently, long-term follow-up data have been rarely reported. Herein, we present a case of disseminated *M. chimaera* infection successfully treated with a clofazimine-containing regimen for 18 months, alongside aortic valve replacement. Importantly, the patient remained free of recurrent symptoms three years after completing antimicrobials.

Case description

A 67-year-old man with a history of native aortic valve endocarditis caused by *Streptococcus agalactiae* treated with aortic valve replacement (AVR) and antimicrobials, presented to an outside hospital two years after his AVR with a three-month duration of malaise, chills, weakness, and sixty-pound weight loss. He also complained of blurry vision. He had no contact with sick individuals and denied traveling outside of the midwestern United States. Vital signs included a blood pressure of 98/82 mmHg, heart rate of 84 beats per minute, respiratory rate of 16 breaths per minute, oxygen saturation of 97 % on room air, and a body temperature of 35.8 °C. Physical examination revealed bilateral leg edema and ocular findings suggestive of chorioretinitis. Laboratory work up revealed a white blood cell count of 2.8×10^9/L (normal range: 3.7–10.5 $\times 10^9$), platelet of 56×10^3/μL (150–400 $\times 10^3$), creatinine of 3.1 mg/dL (0.6–1.2), lactate of 3.6mEq/L (0.5–2.0), aspartate aminotransaminase of 66 U/L (0–40) and alanine aminotransferase of 61 U/L (0−41). Brain computed tomography (CT) was unremarkable. Abdomen and pelvis CT showed splenomegaly with calcified splenic lesions consistent with granulomas. The patient underwent bone marrow aspiration and biopsy to evaluate his pancytopenia, revealing granulomatous changes with negative staining for bacterial, fungal, and mycobacterial organisms in the histopathology specimen.

The patient was treated with vancomycin and cefepime for concern

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of sepsis after multiple sets of blood cultures were obtained. Further diagnostic investigations included a magnetic resonance imaging (MRI) of the brain and a transthoracic echocardiogram (TTE), which showed no abnormalities. A transesophageal echocardiogram (TEE) showed thickening in the aortic root, extending posteriorly onto the aortomitral continuity, and thickening of the right lateral annulus with soft tissue echoes of varying echogenicity. These findings raised concerns of prosthetic valve endocarditis with a root abscess. The cardiovascular surgeons determined that the patient was not a suitable candidate for surgery. Blood cultures remained negative, prompting an investigation for culture-negative endocarditis, which included fungal blood cultures, serum *Tropheryma whipplei* PCR, and serological tests for Bartonella, Brucella, Coxiella, Histoplasma, and Blastomyces, all of which yielded negative results. Additionally, the patient tested negative for human immunodeficiency virus. He was discharged with a plan to continue intravenous ceftriaxone for a total of six weeks to treat culture-negative prosthetic valve endocarditis.

However, an acid-fast bacilli (AFB) blood culture obtained yielded a positive result, prompting the patient's referral to our institution for admission and further treatment. The organism was subsequently identified as *Mycobacterium chimaera*. While awaiting susceptibility testing, the patient was initiated on empirical treatment with clarithromycin, rifabutin, and ethambutol. Moxifloxacin was considered as a fourth drug, but it was not administered due to the patient's prolonged QT interval of 490 ms. During a one-month follow-up, the patient exhibited poor appetite, an additional weight loss of 20 pounds (total of 80 pounds since symptom onset), and acute kidney injury (AKI) with a serum creatinine level of 2.5 mg/dL (baseline Cr 1.5 mg/dL), despite receiving a three-drug regimen. Repeat AFB blood culture remained negative, and susceptibility testing revealed that the organism was susceptible to the antimicrobials the patient was taking. The AKI was attributed to a combination of dehydration and *M. chimaera*-associated nephritis, possibly accompanied by immune reconstitution inflammatory syndrome (IRIS) triggered by the treatment. Intravenous fluids were administered, and the patient was initiated on oral prednisone at a dosage of 60 mg/day in addition to his antimicrobials. Over many weeks, his serum creatinine gradually improved, to the patient's baseline of 1.5 mg/dL. Based on discussions with local and international non-tuberculosis mycobacteria experts, the patient's regimen was transitioned to azithromycin, rifabutin, and ethambutol.

After three months of treatment, the patient was admitted for scheduled aortic valve replacement surgery. At that time, his prednisone dosage had been gradually tapered down to 10 mg/day. The valve replacement procedure was successfully performed without any significant complications. In addition to his three-drug regimen, the patient received intravenous amikacin for a total of 4 weeks, administered perioperatively (2 weeks before and 2 weeks after the surgery). Histopathological examination of the resected prosthetic aortic valve demonstrated an inflammatory infiltrate comprising neutrophils and macrophages, indicative of active and healing endocarditis on the valve's surface (Fig. 1). Beaded acid-fast bacilli were observed on the AFB stain, accompanied by infrequent neutrophils (Fig. 2). Subsequent AFB culture from the vegetation confirmed the growth of *M. chimaera.*

Three months following his surgery, the patient developed optic neuropathy attributed to ethambutol. Consequently, his treatment regimen was modified to include azithromycin, moxifloxacin, and rifabutin, with a planned transition from moxifloxacin to clofazimine once the latter was obtained through an investigational new drug program (IND), with approval from the local Institutional Review Board (IRB). Unfortunately, the patient experienced a rash believed to be associated with moxifloxacin, leading to its discontinuation. In the interim, amikacin was resumed while awaiting the availability of clofazimine. Two weeks later, clofazimine was approved and initiated. The patient remained on four-drug therapy consisting of azithromycin, rifabutin, clofazimine, and amikacin for a total of two months, after which amikacin was discontinued. Subsequently, the patient continued with three drugs (azithromycin, rifabutin, and clofazimine) for an additional 12 months, resulting in a total treatment duration of 18 months from the time of the aortic valve replacement. The decision to discontinue antimicrobial therapy was complex and made after detailed discussions with experts in the field. We used several parameters before stopping antimicrobials and these included absence of any clinical symptoms, recovery of cell counts, negative AFB blood cultures, negative plasma metagenomic sequencing for AFB and negative PET-CT [1]. At the most recent follow-up at our clinic (3 years after the completion of the treatment), he was clinically doing well without any symptoms.

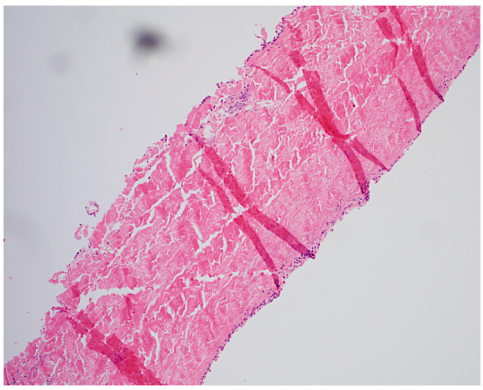

Fig. 1. Hematoxylin and eosin stain (10X objective) of vegetation. Inflammatory infiltrate of neutrophils and macrophages, representing active and healing endocarditis on the surface of the valve.

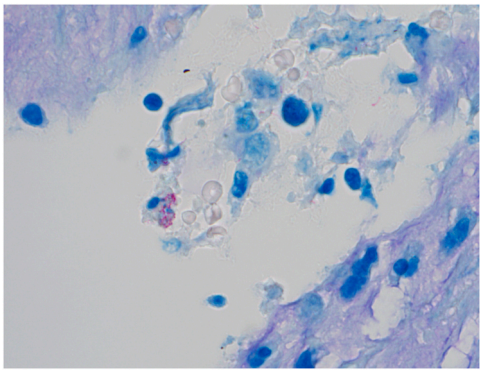

Fig. 2. Acid-Fast Bacillus stain (100X objective) of vegetation. Beaded acid-fast bacilli are evident within rare neutrophils and occasional free bacilli are seen adherent to the valve surface.

Discussion

Mycobacterium chimaera was first described in 2004 by Tortoli and colleagues [2]. *M. chimaera* can contaminate tap water and has been found to grow in water tanks within heater-cooler devices utilized during open heart surgeries [3]. Droplets loaded with *M. chimaera* are released from the contaminated water tanks, spreading an infective bioaerosol with a particle size of < 1 mm in the operating room environment [4,5]. These aerosols can be inhaled and also settle on surfaces, leading to contamination in the operating room environment, including of surgical wounds or of prosthetic materials such as heart valves or vascular grafts. Contamination with *M. chimaera* may be followed by slow growth and biofilm formation on intravascular prosthetic material, leading to dissemination and multisystem involvement with *M. chimaera* infection.

Until recently, *M. chimaera* would have been identified by most laboratories as *M. intracellulare* or *M. avium* complex using commonly

available methods. A study that retrospectively sequenced samples from patients with diagnosed MAC found that 28 % of infections were due to *M. chimaera*, while 54 % and 18 % of previously diagnosed MAC infections were due to *M. avium* and *M. intracellulare*, respectively [6].

Since 2013, more than 180 cases of HCU device–related *M. chimaera* infection have been recognized from Europe, the United States, Canada, and Australia [7,8]. The longest reported time from surgery to presentation of symptoms was more than 6 years. In our case, the patient developed symptoms approximately 2 years after his surgery. Disseminated *M. chimaera* infection can exhibit a wide spectrum of disease including prosthetic valve endocarditis, aortic graft infection or localized thoracic infection, granulomatous nephritis, granulomatous hepatitis, chorioretinitis, multifocal choroiditis, and pulmonary infection, as well as spondylodiscitis, osteoarthritis, and post-sternotomy wound infection. A case series in the United Kingdom (n = 30) revealed that the common symptoms were fever (80 %), malaise (80 %), weight loss (60 %), cough (37 %), and dyspnea (33 %) [9]. Abnormal ophthalmologic findings are common in patients with disseminated *M. chimaera* infection and some experts recommend ocular exams should be performed in all suspected patients [8].

The European Center for Disease Prevention has formulated a case definition for M. chimaera infections associated with open-heart surgery based on three criteria: (i) any of the clinical criteria, including a prosthetic valve or vascular infection, localized infection, and disseminated infection, (ii) an exposure criteria, e.g., having undergone surgery requiring cardiopulmonary bypass in the 5 years prior to the onset of symptoms of infection, (iii) microbiological criteria, e.g., *M. chimaera* detected by culture or identified by DNA sequencing in an invasive sample [10]. Mycobacterial cultures need to be performed on all suspected sample types including blood, tissue, bone, pus, and urine. Culture of *M. chimaera* from peripheral blood is the most common method of microbiological diagnosis. In a case series with 8 infections, 7 of them had a positive blood culture [11].

The American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA), recommend combination antimycobacterial therapy with clarithromycin, rifampin and ethambutol for patients with disseminated *Mycobacterium avium* complex infection [12]. According to the International Society for Cardiovascular Infectious Diseases (ISCVID), *M. chimaera* infection is generally treated with a prolonged course of the same combination of antimicrobials and severe disease may require additional antibiotic therapy with aminoglycosides [13,14]. Amikacin is also recommended as part of the initial regimen in preparation for foreign material removal or replacement [8]. Organisms within MAC are typically susceptible to macrolides and clofazimine with variable susceptibility to rifampin, rifabutin, ethambutol, linezolid, amikacin, moxifloxacin, and ciprofloxacin. However, routine susceptibility testing is recommended only for clarithromycin, as it is the primary drug used for treatment and results correlate well with clinical response [15]. Susceptibility of MAC isolates to moxifloxacin and linezolid are recommended in case of clarithromycin-resistant MAC. Rifampin, rifabutin, ethambutol, amikacin, and streptomycin are also considered clinically useful; however, the role of susceptibility testing for these agents is controversial, as there are often poor correlations between MIC results and treatment outcomes [10]. Clofazimine has shown significant synergistic activity against MAC strains in vitro and may be useful for treatment of *M. chimaera* infections [16]. More recently, in vitro data showed that a combination of bedaquiline and clofazimine may add activity for the treatment of MAC infections [17].

The current recommended duration of therapy for disseminated MAC in non-HIV–infected individuals is 12 months. While the optimal duration of therapy for M. chimaera is unknown, the ISCVID recommends a minimum of 12 months after the first negative blood culture or redo surgery [14]. Additionally, revision surgery with removal of all cardiovascular prosthetic material should be considered [14]. The same guideline also suggests long-term suppressive antibiotic therapy for those who are not candidates for additional cardiovascular surgeries. However, drug-related adverse reactions are reported in 20–40 % of patients with M. chimaera infections [18,19]. Our patient developed acute kidney injury likely from amikacin, and rifampin, optic neuropathy from ethambutol and skin rash from moxifloxacin. Careful monitoring for response to therapy is key to treating disseminated *M. chimaera* infection. Nevertheless, medical therapy often fails to result in clearance even with antibiotic therapy targeted to in vitro sensitivities. The mortality of *M. chimaera* infection related to the Heater-Cooler Unit is extremely high at approximately 46 % in prior reports with a median follow-up of 10 months [7,9,20,21]. Therefore, very limited data is available regarding long term follow up among survivors from *M. chimaera* infection.

In conclusion, we present a case of disseminated *M. chimaera* infection successfully treated with a clofazimine-containing regimen for 18 months, alongside aortic valve replacement. While long-term follow-up has been rarely reported, our patient has remained symptom-free with no signs of recurrence three years after completing antimicrobials. Adverse reactions to medication occur in 20–40 % of patients with *M. chimaera* infections, highlighting the importance of careful therapy monitoring in managing disseminated *M. chimaera* infection. The mortality rate associated with *M. chimaera* infection linked to Heater-Cooler Units is alarmingly high at 46 %. Clofazimine serves as an alternative and effective treatment option for *M. chimaera* infection when first-line drugs cannot be used due to adverse reactions or resistance.

Ethical approval

The local ethical committee approval does not apply in this case.

Conflict

None.

Consent

Written consent was obtained.

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The following information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

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Consent

Studies on patients or volunteers require ethics committee approval and fully informed written consent which should be documented in the

paper.

Authors must obtain written and signed consent to publish the case report from the patient (or, where applicable, the patient's guardian or next of kin) prior to submission. We ask Authors to confirm as part of the submission process that such consent has been obtained, and the manuscript must include a statement to this effect in a consent section at the end of the manuscript, as follows: "Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request".

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Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing, others, who have contributed in other ways should be listed as contributors.

TK wrote a first draft of the manuscript. PS, BF and DD critically reviewed and revised the manuscript. All authors read and approved the final paper.

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CRediT authorship contribution statement

Poorani Sekar: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Daniel Diekema:** Investigation, Writing – review & editing. **Bradley Ford:** Investigation, Writing – review & editing. **Takaaki Kobayashi:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

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