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MAJOR ARTICLE

Updated Experience of *Mycobacterium chimaera* Infection: Diagnosis and Management in a Tertiary Care Center

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Background. Despite safety communications from the Food and Drug Administration (FDA) regarding the outbreak of *Mycobacterium chimaera* infections (MCIs) from contaminated heater-cooler devices, new cases continue to be identified.

Methods. We retrospectively reviewed confirmed cases of MCI that were managed at Mayo Clinic sites (Arizona, Florida, and Minnesota) from 09/2015 to 01/2021. Clinical histories including prior cardiovascular surgery were recorded. Diagnostic workup including ophthalmologic examination, imaging, and laboratory testing was reviewed. Treatment and survival outcomes on follow-up were obtained.

Results. Twelve patients with MCI were included. All patients had aortic valve or graft replacement. Five patients had their surgical procedures following the 10/15/2015 FDA safety communication. The mean time from surgery to symptom onset (range) was 32 (13–73) months. Ten of 11 patients who underwent ophthalmologic examination had chorioretinal abnormalities. Three patients who underwent microbial cell-free deoxyribonucleic acid sequencing tested positive for *M. chimaera,* which was subsequently confirmed with blood culture growth. Echocardiography and positron emission tomography/computed tomography (PET/CT) revealed evidence of prosthetic valve/graft infection in 7/12 (58.3%) and 6/10 (60.0%) of cases, respectively. Seven patients (58.3%) underwent redo cardiovascular surgery. Of these, 1 patient died 2 days postdischarge, 1 experienced spinal osteomyelitis relapse, and another had interval prosthetic valve fluorodeoxyglucose (FDG) uptake on PET/CT suspicious for recurrent infection. Among 4 patients on medical therapy only, 3 expired or transitioned to hospice during follow-up.

Conclusions. MCI continues to occur despite the FDA communications. Incorporation of ophthalmologic examination and use of advanced tools may improve MCI diagnosis. The mortality in these patients is high even with aggressive surgical/medical management.

Keywords. *Mycobacterium chimaera*; nontuberculous mycobacterium; cardiovascular surgery; prosthetic valve endocarditis.

Mycobacterium chimaera is a relatively low-virulent member of the *Mycobacterium avium* complex (MAC), a group of slow-growing nontuberculous mycobacteria (NTM). Contrasting most MAC infections, *M. chimaera* has been closely associated with delayed-onset prosthetic cardiovascular infections acquired through open heart surgery and corresponding disseminated disease [1–3]. Following a series of meticulous investigations by an international collaboration, the source of the outbreak was attributed to *M. chimaera*–contaminated heater-cooler devices (HCDs) used during cardiopulmonary bypass (CPB) [3–7]. Most of the identified cases were traced to LivaNova (London, UK) 3T HCDs, which accounts for ~70% of the worldwide market share. The US Food and Drug Administration (FDA) issued a safety communication in October of 2015 regarding the association between HCDs and *M. chimaera* infections; recommendations for instituting deep-cleaning procedures or replacement of entire HCDs were subsequently released [8]. The annual incidence of *M. chimaera* infections (MCIs) has been estimated at 156–282 cases per year based on data from 10 countries with cardiac surgical valve/graft capability [9]. In 2020, the International Society of Cardiovascular Infectious Diseases published guidelines for preventing and treating MCI related to cardiopulmonary bypass [10].

Despite the release of information regarding MCI and development of mitigation measures, additional MCI cases were identified at our institution over the past few years, many of which were associated with cardiovascular surgeries that postdated the 2015 FDA safety communications. This continued observation of MCI among patients with recent cardiovascular surgery exposure therefore prompted an updated review of our tertiary care institutional experience.

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METHODS

Study Cohort and Clinical Characteristics

This was a retrospective cohort analysis of patients diagnosed with or treated for MCI between 09/2015 and 01/2021 at Mayo Clinic sites (Phoenix, Arizona, Jacksonville, Florida, and Rochester, MN, USA). Demographics, clinical history and presentation, laboratory/pathology testing, imaging, and surgical reports were obtained from the patients' electronic medical records as well as available outside records. Included patients were required to fulfill the diagnostic criteria by Hasse et al.: (1) history of surgery requiring CPB; (2) laboratory testing positivity for *M. chimaera*; (3) clinical signs and symptoms concordant with MCI [10]. Informed consent was obtained from all included patients. The study was approved by the Mayo Clinic Institutional Review Board (18-004096).

Microbiology Testing

Microbiologic diagnosis of MCI was obtained with the following tests: positive mycobacterial blood cultures followed by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF) confirmation of *M. chimaera,* or positive mycobacterial cultures of surgically resected prosthetic valve/graft tissue or biopsies of extracardiac sites followed by MALDI-TOF confirmation of *M. chimaera*. In some cases, the diagnosis was initially made via a microbial cell-free DNA quantitative sequencing blood test (Karius, Redwood City, CA, USA) with positive identification of *M. chimaera* that was subsequently confirmed by blood culture growth positivity [11]. Antimicrobial susceptibility testing for confirmed MCI cases was recorded as well.

Additional Diagnostic Testing

Available imaging findings from modalities including echocardiography, positron emission tomography/computed tomography (PET/CT), cardiac-gated CT, and cardiac magnetic resonance imaging (MRI) were documented. Ocular involvement in patients was determined through the identification of select retinal lesions though a formal funduscopic examination. Histopathology findings from resected prosthetic material or extracardiac biopsy sites were noted.

Management, Follow-up, and Outcomes

Details of treatment strategies pursued were recorded. This included timing and types of antimycobacterial agents used as well as surgical resection of prosthetic cardiac material. Mortality/survival status post-therapy was obtained; for surviving patients with follow-up data, microbiologic clearance/persistence of MCI in both surgical and nonsurgical subgroups was determined where available.

Statistical Analysis

Continuous variables were reported as mean and SD. Categorical variables were reported as number and percentage.

RESULTS

Patient Baseline Characteristics and Clinical Presentations

A total of 12 patients with confirmed MCI were included (Table 1); 3 patients (patients 6, 7, and 8) (Figure 1) were in a previously published series [12]. The mean age at surgery was 64.7 years; most (n = 10; 83.3%) were male. The most common surgical procedure (n = 10; 83.3%) was aortic valve replacement (AVR). Five patients (41.7%) had surgical procedures after the 10/15/2015 FDA safety communication was issued. The mean time from initial cardiac surgery to MCI symptom onset (range) was 32.0 (13–73) months. The most common symptoms at presentation of MCI were weight loss (n = 8; 66.7%) and fatigue (n = 7; 58.3%). Three patients were initially diagnosed with sarcoidosis, and 1 was referred for possible amyloidosis (Figure 1); these diagnoses were ultimately found to be erroneous. The average time to diagnosis (from initial health care presentation) (range) was 5.9 (1–13) months; this was 5.4 months among patients who underwent cardiovascular surgery before 10/15/2015 and 6.6 months for those who had surgery after.

Microbiology Diagnostic Findings

Eleven patients (91.7%) had positive blood cultures for *M. chimaera*. One patient had no growth on blood cultures but underwent redo cardiovascular surgery due to high clinical suspicion

Table 1. Baseline Characteristics and Clinical Presentations of Patients With MCI (n = 12)

Variable	Result
Male sex, No. (%)	10 (83.3)
Mean age at surgery (SD), y	64.7 (5.5)
Cardiovascular surgery type before MCI, No. (%)	
AVR alone	7 (58.3)
AGR alone	1 (8.3)
AVR plus AGR	2 (16.7)
AVR plus LAA closure	1 (8.3)
Composite valve conduit	1 (8.3)
Cardiovascular surgery location by region, No. (%)	
Midwest	9 (75.0)
South	2 (16.7)
Northeast	1 (8.3)
Mean time from surgery to symptom onset (SD), mo	32.0 (18.9)
Mean time from presentation to diagnosis (SD), mo	5.9 (3.8)
Symptoms, No. (%)	
Fever	5 (41.7)
Nightsweats	4 (33.3)
Weight loss	8 (66.7)
Fatigue	7 (58.3)
Anorexia or early satiety	2 (16.7)
Cough	1 (8.3)
Heart failure	1 (8.3)
Altered mental status	3 (25.0)
Disequilibrium	2 (16.7)
Diplopia	1 (8.3)

Abbreviations: AGR, aortic graft replacement; AVR, aortic valve replacement; LAA, left atrial appendage; MCI, *Mycobacterium chimaera* infection.

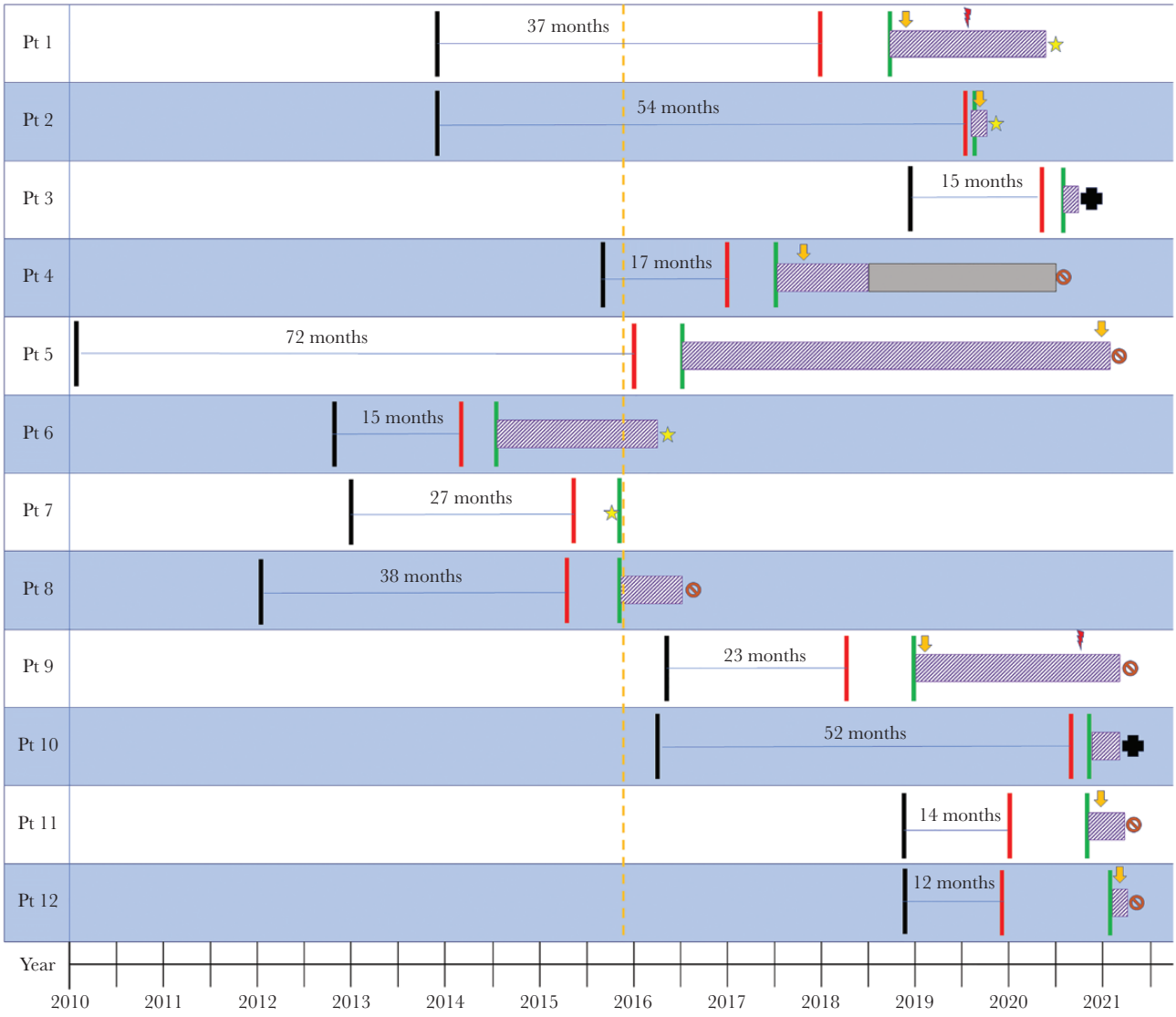

Figure 1. Patient diagnostic and treatment timeline. Black line – date of cardiovascular surgery. Red line – symptom onset. Green line – MCI diagnosis. Orange dotted line – FDA safety communications date. Orange arrow – redo surgery date. Purple shaded bar – antimycobacterial therapy. Gray bar – medication-free period. Yellow star – death. Stop sign – end of follow-up. Cross – hospice. Red lightning – recurrent MCI. Abbreviations: FDA, Food and Drug Administration; MCI, *Mycobacterium chimaera* infection.

(transaminitis, bicytopenia, chorioretinitis); the resected aortic graft grew *M. chimaera* in culture. In addition, 3 patients underwent Karius testing that revealed positivity for *M. chimaera*; mycobacterial blood cultures later became positive for all 3 patients. Two patients had *M. chimaera* grow from bone marrow cultures, 1 had positive sputum culture, and 1 had positive skin biopsy culture. Seven patients underwent redo cardiovascular surgery; among these, all patients had both positive acid-fast bacilli stains and culture growth for *M. chimaera* from their surgical samples.

Antimicrobial susceptibilities for available blood and tissue cultures are included in Supplementary Table 1. Minimum inhibitory concentrations (MICs) ranged from 1 to 8 μg/mL for clarithromycin and from 4 to 16 μg/mL for amikacin (all susceptible).

Cardiovascular Findings

All 12 patients underwent cardiovascular-directed imaging to assess for evidence of endocarditis, often with >1 modality. In brief, prosthetic valve dysfunction/vegetation, aortic root abscess, or pseudoaneurysm was detected for 9 patients (75.0%) on preoperative imaging or intraoperatively (Table 2). However, only 7 patients had convincing evidence of infection on transthoracic or transesophageal echocardiography (58.3%). Of the 10 patients who underwent PET/CT, only 6 (60.0%) demonstrated significant fluorodeoxyglucose (FDG) uptake suggestive of inflammation/infection. Among the 7 patients who underwent redo cardiovascular surgery, 5 had gross abnormalities on the prosthetic valve or native tissue noted by the surgeon.

Table 2. Abnormalities Associated With MCI Organized by Organ System

Organ System/Abnormality	Result
Neurologic	
Normal pressure hydrocephalus	1
Ocular	
Chorioretinal lesions (n = 11 with ophthalmologic exam)	11
Cardiac	
Prosthetic valve dysfunction, thickening, or vegetations	7
Aortic root abscess or pseudoaneurysm	9
Periprosthetic fluid collection	2
Prosthetic FDG uptake (n = 10 with PET/CT)	6
Pericardial effusion	1
Pulmonary	
Ground-glass opacities	2
Lung FDG uptake (n = 10 with PET/CT)	2
Gastrointestinal	
Colonic wall thickening	1
Noncaseating granulomas in duodenum	1
Noncaseating granulomas in liver	1
Hepatomegaly	1
Transaminitis	6
Hematologic	
Anemia	8
Thrombocytopenia	8
Pancytopenia	5
Noncaseating granulomas on bone marrow biopsy	6
Splenomegaly	11
Hemangiophagocytic histiolymphocytosis	1
Immune reconstitution inflammatory syndrome	1
Renal	
Acute or subacute kidney injury	4
Noncaseating granulomas on renal biopsy	2
Orthopedic	
Osteomyelitis	1
Skin	
Noncaseating granulomas on skin biopsy	1

Abbreviations: FDG, fluorodeoxyglucosel; MCI, *Mycobacterium chimaera* infection; PET/CT, positron emission tomography/computed tomography.

Noncardiovascular Findings

Extracardiac organ involvement by *M. chimaera* was common (Table 2). Of 11 patients who underwent ophthalmologic examination, 10 had chorioretinal abnormalities compatible with mycobacterial infection (90.9%); 1 patient had a chronic retinal scar of unclear etiology but no choroidal enhancement. Only 1 patient (patient 12) reported ocular complaints of blurry vision. Most patients (n = 11, 91.7%) had splenomegaly on imaging. Cytopenias were often noted (prompting bone marrow biopsies), as well as transaminitis and renal dysfunction. Biopsies of the liver, kidney, and duodenum were pursued in response to patient symptoms and abnormalities in biomarkers; when performed, they frequently revealed the presence of noncaseating granulomas. One patient presented with hemangiophagocytic lymphohistiocytosis (HLH), and another experienced immune reconstitution inflammatory syndrome (IRIS) during medical therapy.

Management

Apart from 1 patient who was diagnosed with *M. chimaera* retroactively, all other patients were treated with antimycobacterial medications (Table 3). A newer macrolide (clarithromycin/azithromycin), ethambutol, and a rifamycin were used in treated patients; many (n = 8; 66.7%) also received amikacin. Seven patients (58.3%) underwent attempted source control with redo cardiovascular surgery. The duration of medical therapy before surgery ranged from 13 to 1677 days (median, 32 days). Of the 5 patients who did not receive surgery, 1 expired before diagnosis, 3 were deemed inoperable following multidisciplinary discussion, and 1 elected for continued medical therapy given his clinical stability.

Outcomes and Follow-up

Among the 4 patients who received antimycobacterial therapy only, 2 (patients 3 and 10) had documented negative mycobacterial blood cultures after 1 month. One patient (patient 8) transitioned to hospice and did not have follow-up blood cultures. One patient (patient 5) had persistently positive blood cultures for *M. chimaera* for 17 months despite multidrug regimens.

In the surgical subset, 6 patients underwent surgery soon after diagnosis; a representative case (patient 11) (Figure 1) is highlighted in Figure 2. Of these, 4 patients did not exhibit evidence of recurrent infection on follow-up. One patient developed spinal osteomyelitis manifested by new-onset back pain 7 months postoperatively (patient 1), and another had interval-increased FDG uptake on surveillance PET/CT 21 months postsurgery (patient 9), with no specific cardiovascular symptoms at the time; both patients had negative blood cultures postoperatively. Both were treated medically, with the former expiring ~18 months after redo cardiovascular surgery. One patient (patient 5) was treated with antimycobacterial therapy initially for several years with good tolerance; she demonstrated negative mycobacterial blood culture growth after 1 month of treatment. However, the presence of new prosthetic valvular vegetations led to concern for progressive endocarditis, prompting redo cardiovascular surgery. Although no gross abnormalities were noted, surgical cultures returned positive for *M. chimaera*.

At the end of follow-up, 4 patients were deceased (2 of whom underwent redo surgery) and 2 transitioned to hospice.

DISCUSSION

Our institutional experience on MCI diagnosed and/or treated has led to the following conclusions: (1) despite national and international alerts regarding the *M. chimaera* outbreak, disseminated infections following cardiovascular surgical procedures conducted as recently as 2018 are still occurring; (2) diagnosis of MCI is often delayed and remains challenging even with extensive testing; (3) outcomes are poor whether or not surgery for source control is performed.

Table 3. Antimycobacterial Medications Utilized in Patient Cohort

Patient	Clarithromycin/Azithromycin	Ethambutol	Rifampin	Rifabutin	Moxifloxacin	Clofazimine	Amikacin
1	x	x	x			x	x
2	x	x	x				x
3	x	x	x				x
4	x	x		x			
5	x	x		x			
6	x	x	x		x	x	x
7[a]			x				
8	x	x	x				x
9	x	x	x	x			x
10	x	x	x				x
11	x	x	x				x
12	x	x	x				x

Abbreviation: MCI, *Mycobacterium chimaera* infection.

[a]Patient was diagnosed with MCI postmortem.

Even though the source of *M. chimaera* contamination was identified years ago, MCI remains a relevant and challenging problem to address. This was brought forth by an excellent multicenter case series of 28 patients by Julian et al. [13], where trends in clinical presentations and outcomes were largely consistent with our findings. One particularly striking and novel observation from our study is that nearly half of the patients (n = 5; 41.7%) with MCI seen at our institution had their index cardiovascular surgeries after the 2015 FDA safety communication. This finding serves as a sober reminder that MCI is still prevalent and will likely continue to occur; whether this reflects inadequate HCD maintenance or new contamination sources is unclear. At our institution, all HCDs that tested positive for *M. chimaera* were replaced with new HCDs from different manufacturers [14]. However, other centers may not have the resources to test for *M. chimaera* contamination or replace potentially affected HCDs. As such, this leaves open the possibility for MCI to arise from surgeries performed even from just a few years ago. Given that the average lifespan of an HCD is 10 years, patients who require CPB may remain exposed to the low but nonzero risk of MCI through 2024 and beyond should contamination stay unaddressed.

The long latency period from exposure to presentation (average [range], 39.0 [18–78] months) and nonspecific nature of signs/symptoms are characteristics of MCI that have been well reported in previous studies [1, 2, 10, 15]. Indeed, patients presented as late as 6 years after their index cardiovascular surgery in our experience. Furthermore, the constitutional symptoms and multisystemic involvement can steer providers toward other differential diagnoses, notably rheumatologic (sarcoidosis) or hematologic diseases (malignancy); misdiagnosis is particularly likely to occur if providers are unaware of MCI and its strong association with prior cardiovascular surgery. Although echocardiography [16] and more recently PET/CT are traditionally accurate tools for detecting prosthetic valve/graft endocarditis [17, 18], this may not be the case for MCI. As highlighted in a representative case (Figure 2), cardiovascular imaging may not yield convincing evidence of infection, which complicates diagnosis and management significantly. Finally, the indolent growth of *M. chimaera* contributes to the lag time in diagnosis, as mycobacterial cultures (if obtained) will take weeks to yield growth.

Still, there is cause for optimism in terms of improving the diagnostic process. We previously noted a proclivity for ocular involvement in our initial report of MCI in the United States [12], a finding that was verified in an extensive ophthalmologic investigation by Zweifel et al. [19]. In this extended series, almost all patients who underwent ophthalmologic examination had chorioretinal abnormalities, which have been noted with disseminated mycobacterial infections. With a prior history of cardiovascular surgery alongside a clinical syndrome of culture-negative endocarditis or granulomatous disease, assessment for chorioretinal lesions can therefore greatly increase the level of suspicion for MCI. Next, the growing availability of microbial cell-free DNA sequencing, which takes just a few days to result (compared with conventional blood culture methods, which can take several weeks), can speed up the microbiological assessment of *M. chimaera* [11]. Additionally, the test is less susceptible to prior antimicrobial therapy and also allows for hypothesis-free testing in the context of culture-negative endovascular infections. In our study, all 3 patients who tested positive for *M. chimaera* with the Karius assay eventually had positive *M. chimaera* culture growth. A more thorough investigation of the test's sensitivity/specificity is needed, but this finding provides a promising proof of concept. Third, advanced modalities for cardiovascular imaging such as cardiac CT and MRI have emerged as important complementary tools in the detection of infective endocarditis. Multimodal imaging techniques such as cardiac-gated CT, PET/CT, and cardiac MRI can play a significant role in detecting or prognosticating MCI

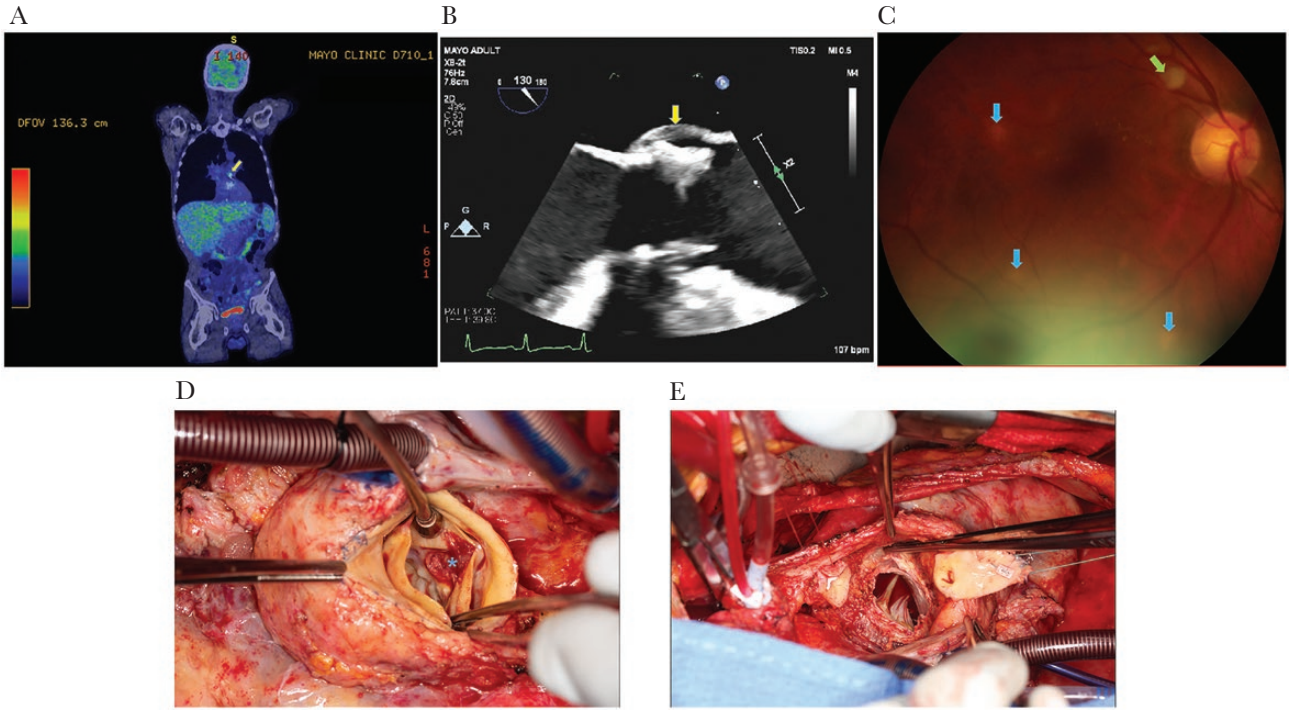

Figure 2. Representative images of diagnostic workup and treatment of a patient with MCI. A 66-year-old man presented with 8 months of fever, nightsweats, and progressive weight loss; he had aortic valve replacement and LAA occlusion 13 months before symptom onset. PET/CT (A) showed focal FDG uptake in the LAA occlusion device (yellow arrow) but no uptake in the aortic valve prosthesis; normal uptake was noted in the liver and spleen. TEE (B) showed minimal thickening in the mitral-aortic intervalvular fibrosa (yellow arrow), inconclusive for endocarditis. Color fundus photography (C) on ophthalmologic examination revealed bilateral chorioretinal lesions (blue arrows); a cotton wool spot associated with the patient's bicytopenia was also noted. Blood cultures eventually returned positive for *M. chimaera*. Redo median sternotomy was performed. A phlegmon (*) was seen in the noncoronary cusp of the aortic valve prosthesis (D). Following resection of the prosthesis, an aortic root abscess with almost complete destruction of the aortic annulus was found (E). Abbreviations: FDG, fluorodeoxyglucose; LAA, left atrial appendage; MCI, *Mycobacterium chimaera* infection; PET/CT, positron emission tomography/computed tomography; TEE, transesophageal echo.

in tandem with echocardiography. Fourth, findings of granulomatous disease often preceded microbiologic diagnosis with clinically driven extracardiac biopsies; hence, MCI should be considered in patients with multisystem granuloma involvement and prior HCD exposure.

Unfortunately, even when MCI is recognized, current treatment outcomes are poor. Slightly more than half of our patient cohort (n = 7; 58.3%) underwent redo cardiovascular surgery for attempted source control. One patient died soon after being discharged from the hospital. Another 2 patients had evidence of infection despite being on multidrug antimycobacterial therapy and having no growth on mycobacterial blood cultures. This may represent subclinical persistence of infection with subsequent seeding into the spine (for patient 1) or radiologic unmasking of recrudescent infection following redo cardiovascular surgery (patient 9). Of the 4 patients treated solely with medical therapy, 3 either expired or transitioned to hospice (75.0%). Contributions to this grim trend include existing advanced comorbidities and age, prolonged time to diagnosis, and inappropriate immunosuppression before MCI confirmation. Furthermore, the recalcitrance of MCI to both medical and surgical therapies is likely rooted in the slow-growing nature of *M. chimaera*, the ability to create a biofilm on prosthetic material (which decreases antimicrobial therapy penetration) [20], and the tendency to colonize other organ systems. As such, it is imperative that FDA HCD maintenance recommendations are strictly adhered to in order to prevent MCI. Information regarding LivaNova's "deep cleaning" service for all 3T HCDs <10 years old as well as vacuum and internal sealing upgrade (ie, Aerosol Collection Set) for reducing the risk of *M. chimaera* airborne transmission can be found in studies published by the Food and Drug Administration and LivaNova [8, 21, 22]. Note, however, that the efficacy of these measures in eliminating infection is unclear [10]; thus, HCDs known or suspected to be contaminated should be promptly removed from service and ideally replaced [14]. Additionally, given the observed suboptimal outcomes, strategies for early diagnosis and prompt surgical intervention are needed, along with improved medical therapeutics against this particular NTM.

Limitations

First, this was a retrospective cohort analysis involving a single tertiary referral institution across 3 physical sites. Hence, the cases reported may not be generalizable to MCIs throughout

the rest of the United States. Second, although this is one of the larger studies of MCI to date, the absolute number included is still relatively small. Third, although we did not identify any patients with MCI who underwent cardiovascular surgery at our institution, we cannot rule out the possibility of MCI being diagnosed elsewhere. Fourth, although surgical centers were notified regarding MCI cases diagnosed at our institution, no feedback regarding measures taken was provided. Finally, long-term survival data for patients who were diagnosed after 2019 are limited given the short follow-up time. Despite the above, the study's findings demonstrate the continued relevance of MCI and the importance of maintaining awareness of it in the years to come.

CONCLUSIONS

MCI remains a relevant concern even among patients who underwent cardiovascular surgery after the release of the FDA safety communications. Tools like ophthalmologic examination, microbial cell-free DNA sequencing, and multimodality cardiovascular imaging can increase the diagnostic speed and accuracy of MCI. Morbidity and mortality remain high despite multidrug medical therapy and redo cardiovascular surgery, which merits further investigation and reporting.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors report no conflict of interest with regards to the present study. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Patient consent. Informed written consent was obtained from all included patients. The study was approved by the Mayo Clinic Institutional Review Board (18-004096).

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