

# The utility of <sup>18</sup>F-fluorodeoxyglucose positron emission tomography with computed tomography in *Mycobacterium chimaera* endocarditis: a case series

Mohamed Dafaalla <sup>1</sup>, Nicholas Weight <sup>1</sup>, Verran Cajic<sup>2</sup>, Uday Dandekar<sup>3</sup>, Kishore Gopalakrishnan<sup>4</sup>, Oludolapo Adesanya<sup>5</sup>, Chen S. Low<sup>5</sup>, and Prithwish Banerjee <sup>1\*</sup>

<sup>1</sup>Department of Cardiology, University Hospitals Coventry and Warwickshire NHS Trust, Clifford Bridge Road, Coventry CV2 2DX, UK; <sup>2</sup>Department of Infectious Diseases, University Hospitals Coventry and Warwickshire NHS Trust, Clifford Bridge Road, Coventry CV2 2DX, UK; <sup>3</sup>Department of Cardiothoracic Surgery, University Hospitals Coventry and Warwickshire NHS Trust, Clifford Bridge Road, Coventry CV2 2DX, UK; <sup>4</sup>Department of Histopathology University Hospitals Coventry and Warwickshire NHS Trust, Clifford Bridge Road, Coventry CV2 2DX, UK; and <sup>5</sup>Department of Radiology, University Hospitals Coventry and Warwickshire NHS Trust, Clifford Bridge Road, Coventry CV2 2DX, UK

For the podcast associated with this article, please visit <https://academic.oup.com/ehjcr/pages/podcast>

Received 4 February 2019; first decision 18 March 2019; accepted 30 October 2019; online publish-ahead-of-print 6 December 2019

## Background

Infective endocarditis secondary to *Mycobacterium chimaera* can present with classical constitutional symptoms of infective endocarditis but can be blood culture negative and without vegetations on transthoracic or transoesophageal echocardiogram. Patients with prosthetic valves are at particularly high risk.

## Case summary

We present two patients who were diagnosed with infective endocarditis secondary to *M. chimaera* infection. They presented similarly with pyrexia of unknown origin and night sweats. Both patients had previously undergone aortic valve replacement; one with a tissue valve and the other with a metallic valve. New cardiac murmurs were evident on auscultation, but clinical examination showed no peripheral stigmata of endocarditis. Transoesophageal echo and transthoracic echo were both unremarkable, as were serial blood cultures. FDG PET CT scan was the key investigation, which showed increased uptake in the spleen beside other areas. Histopathology and mycobacterial cultures confirmed the diagnosis of *M. chimaera* infection in both cases. The first patient completed medical therapy and is now fit and well. However, the second patient unfortunately developed disseminated infection causing death.

## Discussion

The management of *M. chimaera* infective endocarditis is challenging, often with delayed diagnosis and poor outcomes. In the context of negative blood cultures and inconclusive echocardiograms where there remains a high index of suspicion for endocarditis, FDG PET CT scanning can be a crucial diagnostic importance and should be considered early in patients with prosthetic valves.

## Keywords

Infective endocarditis • PET-CT • Mycobacterium • Case series • Echocardiogram

\* Corresponding author. Tel: 44 2476965670, Email: [Prithwish.Banerjee@uhcw.nhs.uk](mailto:Prithwish.Banerjee@uhcw.nhs.uk)

Handling Editor: Timothy C. Tan

Peer-reviewers: Francesca Musella and Hajnalka Vágó

Compliance Editor: Mohammed Majid Akhtar

Supplementary Material Editor: Peregrine Green

© The Author(s) 2019. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

## Learning points

- *Mycobacterium chimaera* endocarditis can present with the usual endocarditis symptoms, i.e. fever, night sweats, swelling, and weight loss.
- Vegetations are usually not detected on echocardiography.
- Typical patients are those who underwent a cardiac surgery for valve replacement several months later.
- The management is of long duration and the outcome is often poor.
- FDG PET CT scanning may help in the diagnostic process.

## Introduction

Infective endocarditis secondary to *Mycobacterium chimaera* can present with classical constitutional symptoms of infective endocarditis but can be blood culture negative and without vegetations on transthoracic or transoesophageal echocardiography.<sup>1,2</sup> Patients with prosthetic valves are at a particularly high risk of this infection and may require further surgical intervention.<sup>3</sup>

with pyrexia of unknown origin and persistent night sweats for 5 weeks, 20 months after mechanical aortic valve replacement. Abdominal examination showed hepatosplenomegaly and an early diastolic murmur consistent with aortic regurgitation was noted. The thromboembolic and autoimmune manifestations of infective endocarditis were not evident on examination. There was no peripheral oedema and the jugular venous pressure was not raised.

His electrocardiogram (ECG) showed sinus rhythm and routine blood tests showed elevated C-reactive protein (CRP) (59 mg/L) (normal <5 mg/L) and normal white cell and neutrophils counts. The total protein was low (51 g/L) (60–83 g/L) and liver enzymes were

## Timeline

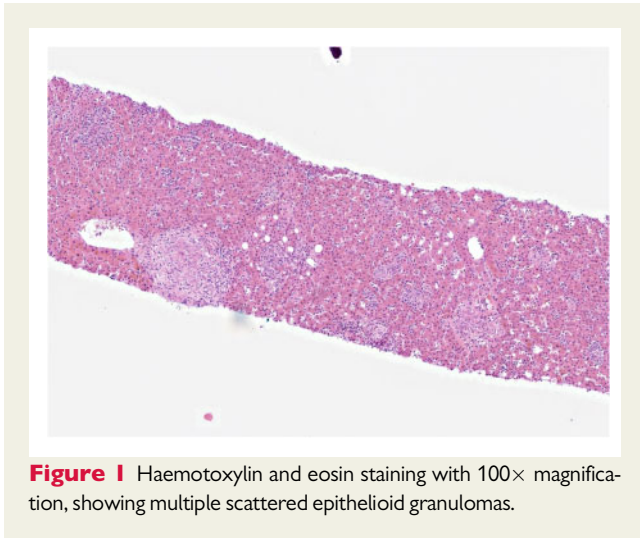
Patient 1	
April 2014	A 49-year-old man underwent mechanical aortic valve replacement for a congenitally bicuspid aortic valve
August 2016	Presentation with pyrexia and night sweats Serial blood cultures negative with inconclusive transthoracic echocardiograms Two negative transoesophageal echocardiograms 2 weeks apart FDG PET CT scan showing focal splenic uptake strongly suggestive of infective endocarditis
September 2016	Increasing C-reactive protein and pyrexia despite medical therapy so underwent 're-do' aortic valve replacement Now clinically well under regular outpatient follow-up
Patient 2	
January 2011	A 64-year-old man underwent a tissue aortic valve replacement for severe aortic stenosis
March 2014	Aortic root replacement
June 2016	Presentation with 2 weeks of pyrexia and night sweats Blood cultures negative and inconclusive transthoracic and transoesophageal echocardiogram undertaken Initially treated empirically as infective endocarditis Suggestion of gallbladder thickening on ultrasound abdomen Switched to intravenous tazocin for presumed biliary source of infection, discharged following completion of course of antibiotics
July 2016	Similar representation 2 weeks later with pyrexia and night sweats, treated empirically for infective endocarditis for full 6 weeks of intravenous antibiotics Underwent FDG PET CT on this admission which showed focal splenic uptake suggestive of infective endocarditis Completed course and discharged with significant improvement
September 2016	Represented to infectious diseases outpatient clinic with erythroderma and recurrent pyrexia. Multidisciplinary team opinion was that this was DRESS syndrome Initially improved with topical steroids and restarted empirical treatment for infective endocarditis, completed course and discharged home
November 2016	Representation 2 months later acutely unwell with disseminated mycobacterium infection, passed away shortly after admission

## Case presentation

### Patient 1

The first patient was a 47-year-old man with history of aortic regurgitation secondary to a congenitally bicuspid aortic valve. He presented

high, especially the Alkaline phosphatase (859 U/L) (30–130 U/L). Hepatitis and HIV viral screens were negative. Initial transthoracic echocardiography showed severe paravalvular aortic regurgitation with no vegetations on the metallic valve; however, there was good biventricular function and no ventricular dilatation. He was started on IV flucloxacillin and gentamicin for suspected endocarditis but

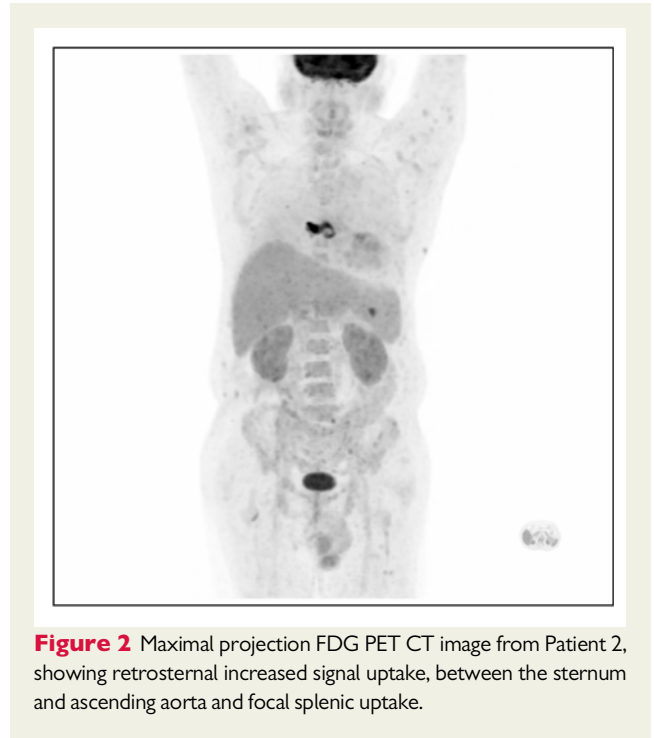


**Figure 1** Haematoxylin and eosin staining with 100× magnification, showing multiple scattered epithelioid granulomas.

blood cultures were negative. Initial CRP was 59 mg/L (<5 mg/L), which remained static for 5 days, vancomycin was added on microbiology advice, resulting in a modest CRP reduction to 33 mg/L (<5 mg/L). Two subsequent transoesophageal echocardiograms carried out a few weeks apart showed no vegetations either, so despite a clinical suspicion of endocarditis this could not be confirmed. Finally, it was felt that an 18F-fluorodeoxyglucose (FDG) positron emission tomography with computed tomography (PET-CT) scan would be valuable to identify the source of infection. This showed mild splenomegaly and focal splenic uptake, which given the clinical context was suggestive of infective endocarditis with a splenic embolic site. Blood cultures were repeated and still showed no growth. The infectious disease team was involved at this point, who requested a liver ultrasound and liver biopsy for histopathology, mycobacterial culture, and polymerase-chain reaction (PCR). The biopsy was requested due to the combination of hepatomegaly on examination and ongoing pyrexia, as part of the pyrexia of unknown origin work-up. The histopathology (Figure 1) showed numerous scattered small epithelioid granulomas that lacked caseous necrosis. These were not specifically associated with portal tracts and were seen throughout the cores (both in the parenchyma and portal tracts).

The diagnosis was difficult and a multidisciplinary team (MDT) approach was needed. The gastroenterology, microbiology, and infectious disease teams were all involved. The case was discussed in both the infectious disease and cardiology MDT meeting. The idea of *M. chimaera* endocarditis first arose in the MDT meeting. Given the persistently raised inflammatory markers, normal transoesophageal echocardiogram but suspicious PET-CT findings, it was felt that this may represent an atypical organism. The similarity in presentation in this case to another in the preceding year also influenced the MDT group to consider *M. chimaera* as a potential underlying cause of this case of infectious endocarditis.

On infectious disease team advice, rifampicin, moxifloxacin, clarithromycin, and ethambutol were prescribed with later introduction of amikacin and withdrawal of clarithromycin due to medication intolerance. He continued medical therapy for approximately 9 months but this failed to control the infection and CRP peaked at 185 mg/L



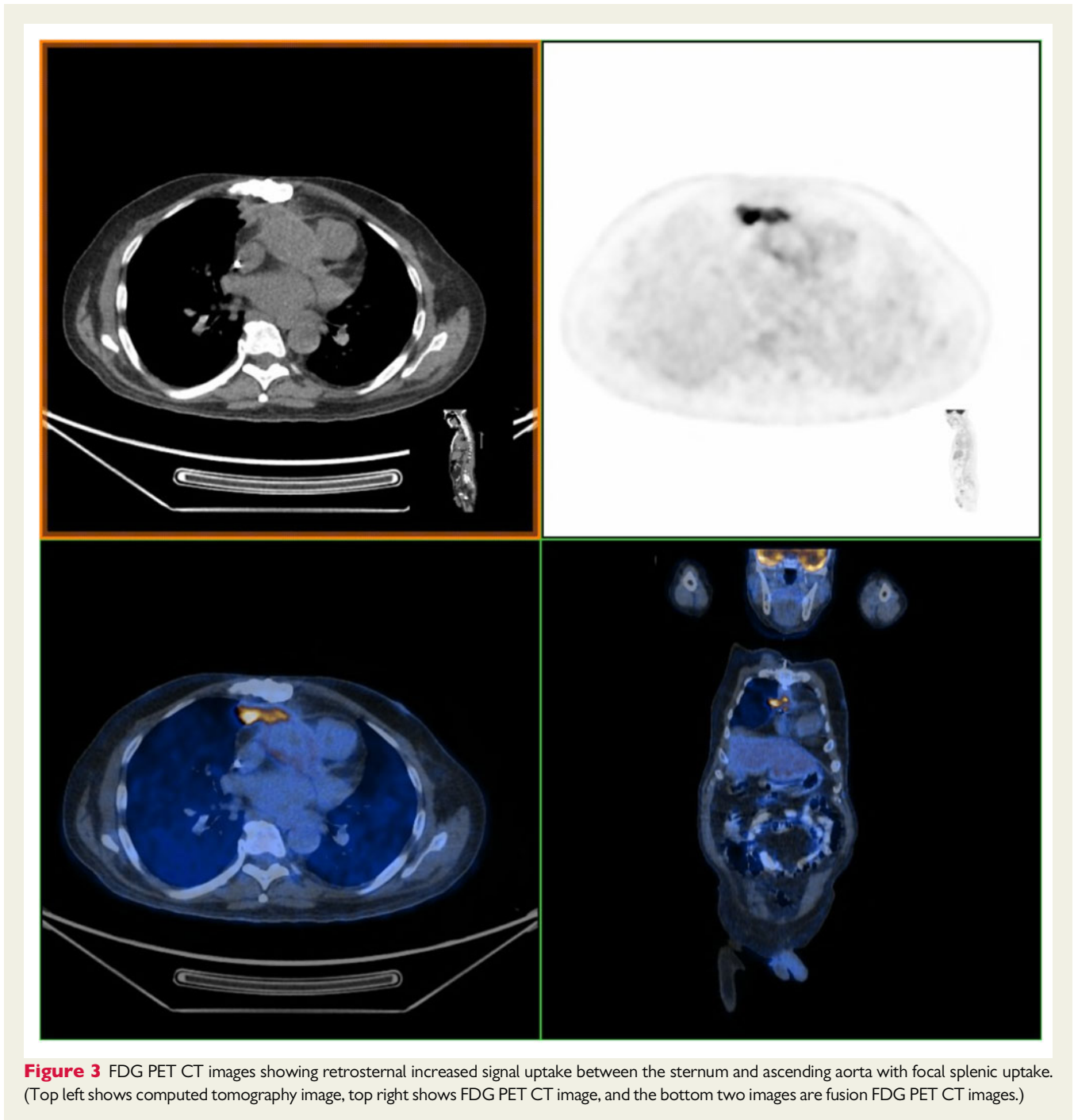
**Figure 2** Maximal projection FDG PET CT image from Patient 2, showing retrosternal increased signal uptake, between the sternum and ascending aorta and focal splenic uptake.

(<5 mg/L). He then underwent a 're-do' mechanical aortic valve replacement in an attempt to remove the infected valve and the mechanical valve was sent to histopathology. This was decided based on the failure of infection control with IV antibiotics following a MDT meeting between the responsible cardiologist, microbiologist, and cardiothoracic surgeon who had performed the original valve surgery. He developed complete heart block post-operatively and permanent pacemaker implantation was performed. Aortic mechanical valve microscopy (of the removed valve) showed moderate numbers of acid fast bacilli and the *M. chimaera* species was isolated in the mycobacterium culture. Antimicrobial therapy towards mycobacteria was restarted after the operation for a 12-months course and the patient showed significant improvement without spiking temperatures. He has now been followed-up for over 3 years and has made a full recovery with his most recent annual transthoracic echo showing only mild left ventricular dilatation and preserved biventricular function.

## Patient 2

The second patient was a 64-year-old man who presented similarly, with 2 weeks of intermittent pyrexia and profuse night sweats. He had a tissue aortic valve replacement for severe aortic stenosis 5 years prior to presentation. He underwent aortic root replacement 2 years later. There were no localizing symptoms. On examination, he had an ejection systolic murmur heard throughout the precordium with a valvular click noted. Examination showed no peripheral stigmata of endocarditis.

The ECG showed sinus rhythm and chest X-ray was normal. Full blood count and renal function were normal. Liver enzymes were slightly elevated without jaundice or hypoalbuminaemia. The CRP was elevated (47 mg/L) (<5 mg/L). All blood cultures were negative



**Figure 3** FDG PET CT images showing retrosternal increased signal uptake between the sternum and ascending aorta with focal splenic uptake. (Top left shows computed tomography image, top right shows FDG PET CT image, and the bottom two images are fusion FDG PET CT images.)

and a sample for mycobacterial culture was sent. HIV and hepatitis screen were negative. Transthoracic and transoesophageal echocardiography showed no vegetations. Abdominal ultrasound showed a thickened gallbladder wall and one small gallstone. CT thorax, abdomen, and pelvis excluded the presence of malignancy or abscess as the cause of the pyrexia.

An FDG PET CT scan was performed which showed a retrosternal soft tissue density/collection involving the pericardium and linear increased uptake was noted in the ascending aorta and root (Figures 2 and 3). This mass was felt to represent an abscess. There

were also metabolically active areas in the right upper lobe and focal splenic uptake. The mycobacterium blood culture isolated a *Mycobacterium avium* intracellular type organism which was identified later as *M. chimaera* infection, and diagnosis of infective endocarditis secondary to *M. chimaera* was established.

Patient 2 was initially treated as endocarditis and started on intravenous flucloxacillin, rifampicin, and gentamicin. Based on the equivocal abdominal ultrasound result, microbiologists briefly advised treating with intravenous piperacillin–tazobactam for suspected cholangitis. There was no right upper quadrant tenderness however and

clinical suspicion of cholangitis was low. He continued to spike temperatures prompting the addition of doxycycline to cover for atypical bacterial infection. His temperature settled and he was discharged with infectious diseases team outpatient follow-up in 2 weeks. Over the follow-up period, he reported rigors and night sweats. The diagnosis of *M. chimaera* infective endocarditis was eventually established based on the results of the PET scan and the mycobacterial blood cultures.

He was commenced on rifampicin, ethambutol, and clarithromycin. His temperatures had settled and his night sweats reduced in frequency and intensity. However, his appetite remained poor and he continued to lose weight. On follow-up with the infectious disease consultant, he complained of dysphagia and ongoing weight loss. He also developed an extensive rash over his arms, legs, and back. The infectious disease team felt this was medication-related and decided to stop all antibiotics temporarily until the rash resolved.

After stopping all medications, he continued to feel unwell and shivery with myalgia and a diffuse itchy rash. He became persistently pyrexial and developed diffuse erythroderma. The patient was admitted to hospital, received topical steroids, improved and was discharged after a week. This presentation was discussed in the multidisciplinary infectious disease meeting and diagnosed as DRESS syndrome secondary to clarithromycin. The rash completely resolved after 1 month. The patient was then admitted for reintroduction of antimicrobial therapy for *M. chimaera* infection and discharged without complications.

After 2 months, the patient developed gradually worsening dysphagia. Swallowing assessment did not show structural abnormality. His barium swallow was normal, and CT scan of the chest, abdomen, and pelvis showed new diffuse parenchymal lung shadowing with new significant splenomegaly. A diagnosis of disseminated *M. chimaera* infection was then made. An honest and thorough discussion with the patient and family about the situation was held to discuss his poor prognosis and poor response to therapy as well as a ceiling of care. In his case repeat cardiac surgery to remove the infected valve was not feasible as he had undergone two previous cardiac operations; a third operation was felt to be too high a risk. The patient expressed the wish to die at home. After discussion with the palliative care team, a plan for care of the dying person was set up. He died almost 1 year after the initial presentation.

## Discussion

The presenting symptoms of *M. chimaera* infection are usually fever, shortness of breath, fatigue, and weight loss.<sup>1,2</sup> The non-specific symptoms, the negative results of echocardiography, deranged liver enzymes, and blood culture limitations can make the diagnosis of *M. chimaera* infection extremely difficult.<sup>1,2,4</sup> For example, one of our patients discussed was initially treated as cholangitis, and in another case report a presumptive diagnosis of sarcoidosis was made and the patient discharged on oral prednisolone before the results of repeated blood culture and bone marrow culture revealed the organism.<sup>1</sup> Misdiagnosis could cause significant harm if immunosuppressive treatment is used in patients with active infection. This was not an isolated case and there have been multiple cases of a diagnosis of

sarcoidosis being made initially before the underlying *M. chimaera* has been found.<sup>5</sup>

The outcome of *M. chimaera* infection can be devastating. In a study of 10 patients with disseminated *M. chimaera* infection subsequent to open-heart surgery at three European Hospitals, eight patients had therapy failure and five patients died.<sup>2</sup> In the same study, all patients who were previously considered inoperable due to presumptively high perioperative mortality had to go for immediate cardiothoracic intervention following the dissemination of the infection.<sup>2</sup> The high mortality rate among patients with disseminated infection brings to light the impact of this infection on patient risk stratification for cardiothoracic surgery.

*Mycobacterium chimaera* is a *Mycobacterium avium* complex (MAC) species that has been thought to have relatively low virulence.<sup>3,6</sup> Two prosthetic valve infections outbreaks of *M. chimaera* and associated disseminated infection were reported in the literature, after thorough epidemiologic and molecular analysis, the source of the infection was found to be the heater-cooler unit used for cardiac bypass procedures.<sup>7,8</sup> These outbreaks were reported initially in the USA, with subsequent clusters reported elsewhere.<sup>7</sup> Further analysis showed that the original source of contamination was the manufacturing facility of the implicated heater-cooler devices (Stockert 3T).<sup>9</sup> These findings encouraged the Food and Drug Administration and Centers for Disease Control and Prevention in the USA to make several recommendations to decrease the risk of additional *M. chimaera* infections.<sup>10</sup> As a result, any Stockert 3T heater-cooler device that has tested positive for *M. chimaera* or was associated with known *M. chimaera* infections and their accessories were removed. Despite the overall low risk of *M. chimaera*, providers of patients who have undergone cardiac surgery should be aware of the possibility of *M. chimaera* infection especially if they develop clinical features compatible with disseminated mycobacterial disease. We do now know that patients who have undergone cardiothoracic surgery are at significantly higher risk of *M. chimaera* compared with the general population, and that this risk can be both early post-operative or a later, more insidious presentation.<sup>7,11</sup> There is not yet consensus regarding optimal antimicrobial therapy in the treatment of *M. chimaera* infective endocarditis, but it likely involves a combination of clarithromycin, ethambutol, and rifabutin, with particular susceptibility to clarithromycin.<sup>2</sup> With increasing volume of cardiothoracic surgery in an increasingly frail and comorbid population, the decision for further cardiothoracic intervention in these patients is often a challenging decision. However, there is growing thought that early surgical discussion with view to removal of infected prosthetic material may be essential for successful treatment of the underlying infection.<sup>12</sup>

However, there are limitations, one particular problem with the use of FDG PET CT in prosthetic valve infective endocarditis is in patients who are in the first 3 months post-operatively, where there is an inability to differentiate between infective endocarditis and normal post-operative changes.<sup>13</sup> FDG PET CT scanning can assist in making an early diagnosis of endocarditis in this setting of negative bacterial cultures and no visible vegetations. Its growing role in the diagnosis of infective endocarditis is reflected by the inclusion in the European Society of Cardiology (ESC) modified diagnostic criteria for infective endocarditis 2015.<sup>14</sup>

## Lead author biography



Mohamed Dafaalla is a core medical trainee (CT1) in Sheffield Teaching Hospitals NHS Foundation Trust, South Yorkshire. He completed MSc in Molecular Medicine, Institute of Endemic Diseases, Sudan and MBBS in University of Khartoum, Sudan.

## Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

## Acknowledgements

We would like to thank the involved patients and/or their next of kin for their consent to be featured in this case series.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** none declared.

## References

1. Tan N, Sampath R, Abu Saleh OM, Tweet MS, Jevremovic D, Alniemi S, Wengenack NL, Sampathkumar P, Badley AD. Disseminated *Mycobacterium chimaera* infection after cardiothoracic surgery. *Open Forum Infect Dis* 2016;**3**: ofw131.
2. Kohler P, Kuster SP, Bloemberg G, Schulthess B, Frank M, Tanner FC, Rössle M, Böni C, Falk V, Wilhelm MJ, Sommerstein R, Achermann Y, ten Oever J, Debast SB, Wolfhagen MJHM, Brandon Bravo Bruinsma GJ, Vos MC, Bogers A, Serr A, Beyersdorf F, Sax H, Böttger EC, Weber R, van Ingen J, Wagner D, Hasse B. Healthcare-associated prosthetic heart valve, aortic vascular graft, and disseminated *Mycobacterium chimaera* infections subsequent to open heart surgery. *Eur Heart J* 2015;**36**:2745–2753.

3. Jaworski R, Naumiuk Ł, Paczkowski K, Formella D, Pek R, Zieliński J, Haponiuk. *Mycobacterium chimaera*—a new threat for cardiac surgical patients? *Kardiochir Torakochirurgia Pol* 2017;**14**:22–26.
4. Achermann Y, Rössle M, Hoffmann M, Deggim V, Kuster S, Zimmermann DR, Bloemberg G, Hombach M, Hasse B. Prosthetic valve endocarditis and bloodstream infection due to *Mycobacterium chimaera*. *J Clin Microbiol* 2013;**51**: 1769–1773.
5. Ganatra S, Sharma A, D'Agostino R, Gage T, Kinnunen P. *Mycobacterium chimaera* mimicking sarcoidosis. *Methodist DeBakey Cardiovasc J* 2018;**14**:301–302.
6. Tortoli E, Rindi L, Garcia MJ, Chiaradonna P, Dei R, Garzelli C, Kroppenstedt RM, Lari N, Mattei R, Mariottini A, Mazzarelli G, Murcia MI, Nanetti A, Piccoli P, Scarparo C. Proposal to elevate the genetic variant MAC-A, included in the *Mycobacterium avium* complex, to species rank as *Mycobacterium chimaera* sp. nov. *Int J Syst Evol Microbiol* 2004;**54**:1277–1285.
7. Chand M, Lamagni T, Kranzer K, Hedge J, Moore G, Parks S, Collins S, del Ojo Elias C, Ahmed N, Brown T, Smith EG, Hoffman P, Kirwan P, Mason B, Smith-Palmer A, Veal P, Lalor MK, Bennett A, Walker J, Yeap A, Isidro Carrion Martin A, Dolan G, Bhatt S, Skingsley A, Charlett A, Pearce D, Russell K, Kendall S, Klein AA, Robins S, Schelenz S, Newsholme W, Thomas S, Collens T, Davies E, McMenamin J, Doherty L, Peto TEA, Crook D, Zambon M, Phin N. Insidious risk of severe *Mycobacterium chimaera* infection in cardiac surgery patients. *Clin Infect Dis* 2017;**64**:335–342.
8. Williamson D, Howden B, Stinear T. *Mycobacterium chimaera* spread from heating and cooling units in heart surgery. *N Engl J Med* 2017;**376**:600–602.
9. Perkins KM, Lawsin A, Hasan NA, Strong M, Halpin AL, Rodger RR, Moulton-Meissner H, Crist MB, Schwartz S, Marders J, Daley CL, Salfinger M, Perz JF. Notes from the field: *Mycobacterium chimaera* contamination of heater-cooler devices used in cardiac surgery—United States. *MMWR Morb Mortal Wkly Rep* 2016;**65**:1117–1118.
10. HAN Archive—00397 | Health Alert Network (HAN). 2018. <https://emergency.cdc.gov/han/han00397.asp> (17 July 2018).
11. Sax H, Bloemberg G, Hasse B, Sommerstein R, Kohler P, Achermann Y, Rössle M, Falk V, Kuster SP, Böttger EC, Weber R. Prolonged outbreak of *Mycobacterium chimaera* infection after open-chest heart surgery. *Clin Infect Dis* 2015;**61**:67–75.
12. Asadi T, Mullin K, Roselli E, Johnston D, Tan CD, Rodriguez ER, Gordon S. Disseminated *Mycobacterium chimaera* infection associated with heater-cooler units after aortic valve surgery without endocarditis. *J Thorac Cardiovasc Surg* 2018;**155**:2369–2374.
13. Sarrazin JF, Trottier M, Tessier M. Accuracy of PET/CT for detection of infective endocarditis: where are we now? *J Nucl Cardiol* 2017;doi:10.1007/s12350-017-1126-2.
14. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, lung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL; ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015;**36**:3075–3128.