

# Successful treatment of healthcare-associated *Mycobacterium chimaera* prosthetic infective endocarditis: the first Spanish case report

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## Background

Since 2011, several cases of health care-related disseminated *Mycobacterium chimaera* infection outbreaks have been reported subsequent to cardiac surgery. Diagnosis is difficult and the prognosis is extremely poor despite long-term antibiotic treatment and surgery.

## Case summary

We report a Spanish case of *M. chimaera* infective endocarditis (IE) with disseminated infection. The patient was treated with long-term antibiotic therapy, valve replacement, and the novel use of interferon-gamma as adjuvant therapy. In addition, [<sup>18</sup>F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) was used in combination with computed tomography (CT) to facilitate the diagnosis as well as to determine the duration of antibiotics and success of treatment.

## Discussion

Diagnosing *M. chimaera* IE is difficult and requires a high index of clinical suspicion. Controlling the infection is even more difficult. Interferon-g used adjuvant to surgery and antibiotic therapy could be useful in achieving this goal. Given that the appropriate duration of antibiotics is unknown, FDG PET/CT could also be a valuable tool for determining when antibiotic therapy can be withdrawn.

## Keywords

Case report • Infective endocarditis • *Mycobacterium chimaera* • Interferon-gamma 1b • <sup>18</sup>Fluorodeoxyglucose positron emission tomography combined with computed tomography • Aortic valve surgery

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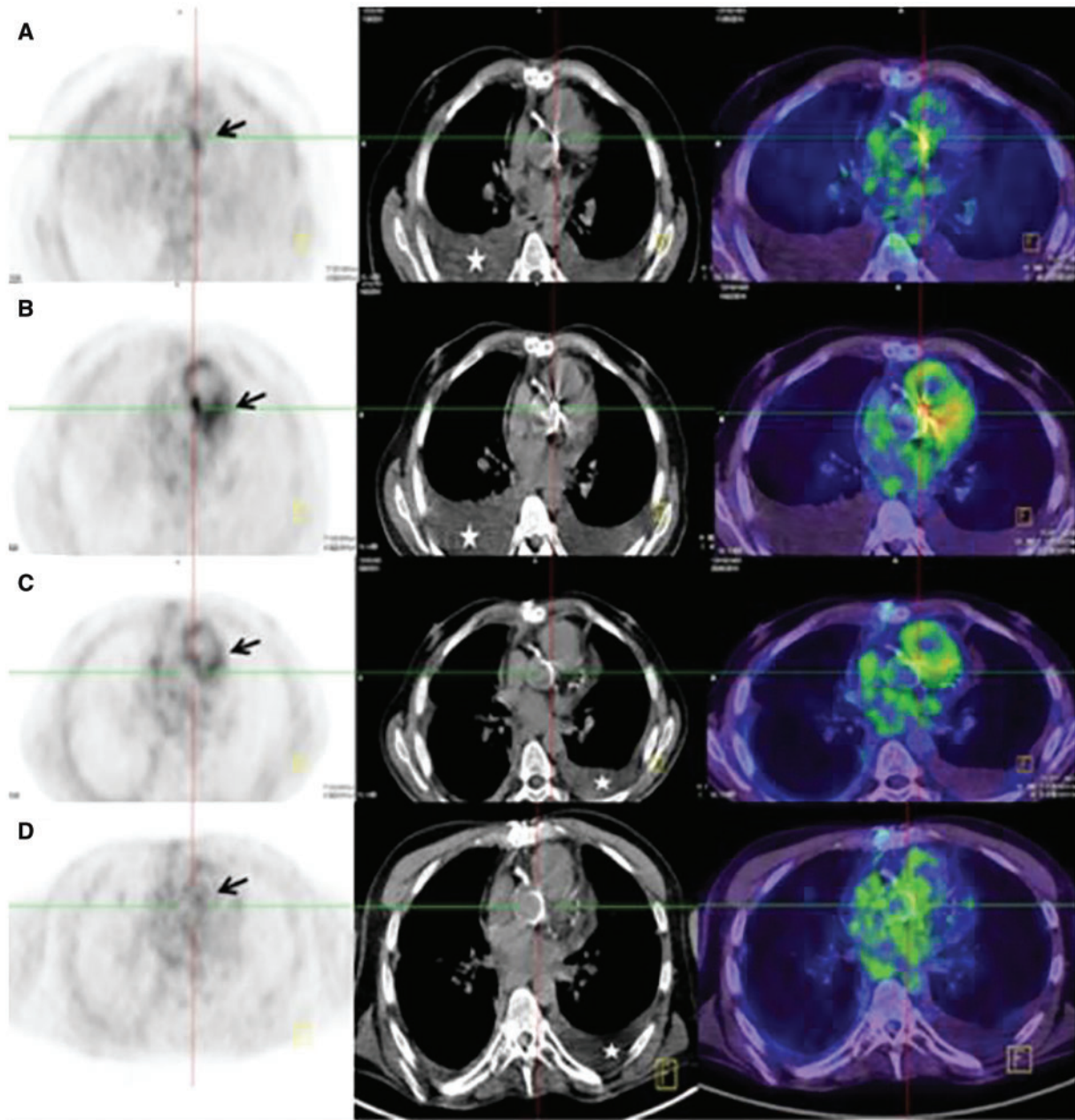
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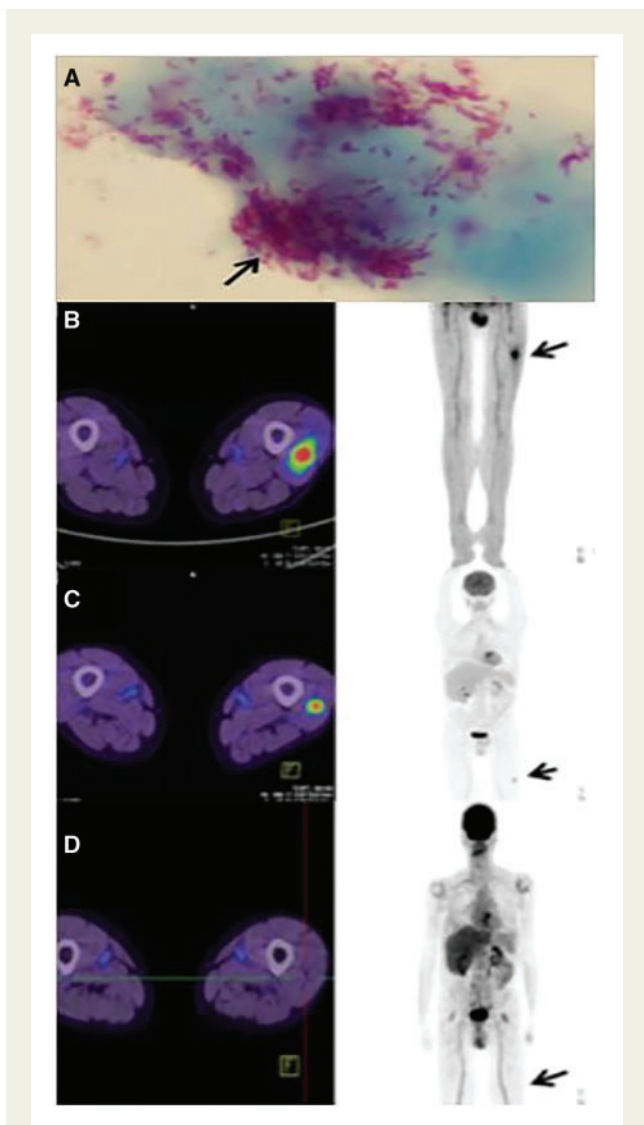




**Figure 1** [ $^{18}\text{F}$ ]-fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG-PET/CT). (A) FDG-PET, CT, and PET/CT fusion images during first admission showing focal uptake in the anterior surface of the prosthetic aortic valve (crossmark). Bilateral pleural effusion is also present (star). (B) FDG-PET, CT, and PET/CT fusion images during second admission, 8 months later, showing increased intensity of the FDG deposit in the aortic valve (crossmark). Again, persistent bilateral pleural effusion is evident (star). (C) FDG-PET/CT study 3 months after aortic valve replacement. There is no evidence of pathological uptake affecting the aortic valve. A diffuse uptake in the heart chamber walls was noted due to physiological incorporation of FDG. Mild right pleural effusion persisted (star). (D) FDG-PET, CT, and PET/CT fusion images performed before stopping the antibiotic treatment, 13 months after aortic valve replacement. There was no uptake in the prosthetic valve. Mild right pleural effusion was still present (star).

using a Siemens Biograph 6 PET/CT scanner (Siemens AG, Munich). A myocardial uptake suppression protocol was applied consisting of a low-carbohydrate/high-fat/free protein diet (started 24–48 h prior to the study) followed by fasting for 16 h. After a blood glucose analysis ( $<200$  mg/L),  $370 \pm 30$  megabecquerels of FDG were

administered. Images were obtained for 3 min/bed position 50 min after the intravenous radiotracer injection, and selective cardiac images were acquired immediately after for 10 min/bed position. The images showed uptake in the aortic bioprosthesis (Figure 1A). As a result, empirical treatment for blood culture-negative IE was initiated



**Figure 2** (A). Ziehl-Neelsen stain showing the presence of numerous acid-fast bacilli in the explanted aortic bioprosthesis infected with *Mycobacterium chimaera*. (B) FDG-PET/CT fusion images and maximum intensity projection of the inferior limbs showing a high intensity focal FDG uptake in muscular tissue of the left thigh (arrow). (C) FDG-PET/CT fusion images and maximum intensity projection of the whole body 3 months after aortic valve replacement showing the persistence of muscle uptake, but with decreased intensity (arrow). (D) FDG-PET/CT fusion images and maximum intensity projection of the whole body 13 months after aortic valve replacement. Absence of uptake in the thigh (arrow).

and serological studies were performed for fastidious bacteria and fungi. Nevertheless, the patient worsened. He persisted with constitutional symptoms (high temperature, night sweats, and weight loss) and developed signs of heart failure (HF) which required intravenous diuretics. In addition, persistent lymphopenia, thrombocytopenia (58 000 cell/ $\mu$ L; normal range 150 000–400 000 cell/ $\mu$ L), and anaemia (8 g/dL; normal range 12–17 g/dL) rapidly appeared.

As part of the lymphopenia study, on one hand, a flow cytometry analysis (FACScalibur flow cytometer, BD Bioscience, CA, USA) showed low T lymphocyte CD4<sup>+</sup> titers (104 cells/mL) with appropriate cytokine production typical of an immune-competent system. On the other hand, a bone marrow biopsy found non-caseating granulomas, which were also found in a liver biopsy. Based on these findings, empirical treatment for tuberculosis was started.

A week later, *Mycobacterium avium* complex (MAC) susceptible to macrolides and aminoglycosides were identified in urine and bone marrow cultures. With the diagnosis of disseminated MAC disease, antibiotic treatment was commenced with clarithromycin (500 mg orally twice daily), rifampicin (600 mg orally once daily), ethambutol (800 mg orally once daily), and prednisone (1 mg/kg intravenously once daily). With this new treatment the patient began to improve.

Taking into account the absence of other findings suggesting IE, it was considered that the prosthetic uptake seen in the FDG PET/CT image was a false positive image. Based on his clinical stability, in September 2015 the patient was discharged for outpatient management.

In November 2015, the patient still presented asthenia, lymphopenia, and occasional mild fever. MAC was still present in blood cultures and cotrimoxazole (800/160 mg orally every 48 h) was added to the treatment. The patient again suffered deterioration in renal function. A renal biopsy resulted in the diagnosis of interstitial nephritis (no granulomas were found). Moreover, the patient developed paraesthesias in his lower limbs, which gradually increased in intensity. After discarding other causes, ethambutol-induced peripheral neuropathy was suspected and ethambutol treatment was withdrawn.

In February 2016 (1 month after ethambutol withdrawal), the patient was again admitted due to increased temperature (38.5°C) and the appearance of a nodule in his left thigh. Laboratory tests showed a significant increase in NT-proBNP (12 500 pg/mL) and CRP (150 mg/L) as well as significant worsening in thrombopenia (50 000 platelets/ $\mu$ L), anaemia (8.5 g/dL) and renal function (GFR 35 mL/min/ $m^2$ ). The TOE showed more thickening around the aortic bioprosthesis than the previous one. The FDG PET/CT was repeated and showed pathological uptake in the aortic prosthesis and the nodule in his thigh (Figures 1B and 2B).

One week later, microbiologists identified the strain of MAC in previous blood and urine cultures (August and November 2015). They identified *M. chimaera* using GenoType NTM-DR (HAIN Laboratories, Nehren, Germany), Random Amplified Polymorphic DNA (RAPD), and Restriction Fragment Length Polymorphism (RFLP), leading to the diagnosis of disseminated disease, and IE due to *M. chimaera*.

Antibiotic treatment was initiated with amikacin (750 mg intravenously once daily) and levofloxacin (500 mg orally once daily) while maintaining clarithromycin and rifampicin. Amikacin levels were satisfactorily maintained within the target of 1–8 mcg/mL (trough) and 20–30 mcg/mL (peak). Despite persisting neuropathy, ethambutol was reintroduced. The case was reported to the Spanish Public Health authority.

In March 2016 (after 1 month on appropriate antibiotic treatment), the patient successfully underwent aortic valve replacement with a mechanical prosthesis. *Mycobacterium chimaera* was isolated in



the aortic bioprosthesis (Figure 2A). However, the suspected mycobacterial abscess in the thigh was not surgically removed because it was diminishing in size and excision was deemed to be technically difficult.

Unfortunately, after surgery the patient still presented high temperature, HF, pancytopenia and renal impairment. Antimicrobial therapy was increased by adding cefoxitin 2 g/day intravenously. Nevertheless, the infection data persisted in spite of blood cultures being *M. chimaera* negative. Hence, a decision was taken to use interferon-gamma 1b (INF-g) which was based on literature reports concerning the use of INF-g in patients with idiopathic CD4<sup>+</sup> lymphopenia (ICL) as adjuvant therapy in refractory disseminated MAC disease.<sup>13,14</sup> INF-g was initiated in mid-April 2016 at doses of 90 mcg (50 mcg/m<sup>2</sup>) three times/week. The INF-g was well tolerated; the patient only experienced mild headache, myalgia, and mild fever after the administration of each dose. The patient began to improve and peaks of high fever disappeared. Due to persistent paraesthesia, ethambutol was suspended and cotrimoxazole was reintroduced.

In May 2016, after a few weeks of clinical stability, the patient was discharged. He developed tinnitus and mild hearing loss as a side effect of amikacin.

The FDG PET/CT was repeated in June 2016 (3 months after cardiac surgery). The images showed no uptake in the aortic prosthesis (Figure 1C). However, the uptake in the suspected thigh abscess remained (Figure 2C). INF-g treatment was suspended after 14 weeks had been completed.

A further FDG PET/CT was performed before ending the antibiotic treatment (13 months after the first negative blood cultures). The images showed no uptake in the aortic prosthesis or the thigh (Figures 1D and 2D). The antibiotic treatment was subsequently terminated.

In July 2017, the patient was afebrile and blood/urine cultures remained negative after 5 months without antibiotic treatment. Thrombopenia and anaemia remitted and lymphopenia slightly improved. However, peripheral neuropathy, slight deafness, and tinnitus still remained as a consequence of drug toxicity.

Unfortunately, in September 2017 the patient was admitted due to confirmed *S. aureus* methicillin sensitive prosthetic IE. The clinical course was complicated, and he finally died due to multiple organ failure in October 2017. Cultures of blood, urine, and bone marrow were *M. chimaera* negative. Necropsy findings confirmed the absence of *M. chimaera* infection.

## Discussion

Firstly, this case illustrates the diagnostic challenge presented by *M. chimaera* IE and disseminated infection, which are frequently misdiagnosed because extra-cardiac manifestations often precede signs of IE (as in the case presented here).

*Mycobacterium chimaera* infection should be suspected in patients with a prior history of cardiac surgery with fever and other systemic involvement data (cytopenia, hepatitis, nephritis, arthritis, chorioretinitis, and vasculitis).<sup>1</sup> Moreover, *M. chimaera* requires culturing in specific media, in the same way as other nontuberculous mycobacteria.<sup>15</sup> Thus, clinical suspicion is essential and physicians

should be aware of *M. chimaera* IE in order to obtain an early diagnosis. Accordingly, the European Center Disease Control published a protocol for *M. chimaera* IE detection and advised considering mycobacteria testing in cases of blood culture-negative IE in patients who have undergone open-heart surgery.<sup>16,17</sup> In relation to diagnostic imaging tests, it should be noted that traditional echocardiography diagnostic imaging criteria have shown lower sensitivity in prosthetic IE. Therefore, in cases of possible/rejected IE according to traditional criteria but with high clinical suspicion, the latest guidelines recommend the use of FDG PET/CT. Any abnormal activity detected by FDG PET/CT around the implantation site in prostheses implanted more than 3 months previously should be considered a major indicator of IE. The abnormal activity around the site of implantation detected by 18F-FDG PET/CT in prosthesis implanted for >3 months, should be considered a major criterion of IE. This allows to reclassify them in definite or rejected IE, with greater sensitivity than echocardiography, thus decreasing the number of doubtful cases, as we did in this case.

Secondly, this case reflects the difficulty in successfully controlling disseminated infection. In fact, uncontrolled infection is the main cause of mortality, which occurs in more than 50% of reported cases.<sup>1</sup> Because of its rarity, the most appropriate antibiotic regimen is unknown and is based on recommendations for disseminated MAC disease.<sup>16</sup> Removal of infected material is essential because biofilm formation hampers antibiotic effectiveness, and at least 2–4 weeks of full antibiotic treatment is recommended prior to surgery, nevertheless, this time is not well established.<sup>1</sup>

Unfortunately, in this case the infection could not be controlled with standard treatment (surgery plus antibiotic treatment). In light of this, we relied on literature reports which described the use of INF-g in patients with idiopathic CD4<sup>+</sup> lymphopenia (ICL) as adjuvant therapy in refractory disseminated MAC disease.<sup>18</sup> Patients with ICL present defective INF-g and tumour necrosis factor (TNF) production which lead to impaired cellular immunity that favours disseminated mycobacterial infections. The administration of INF-g enhances the release of endogenous INF-g and TNF, thereby improving cellular immune response. The dose used was the same as that reported in ICL patients (50 µg/m<sup>2</sup> three times a week).<sup>13,14</sup> Although lymphopenia seemed to be due to infection (it was absent before 2014) and cytokine production was normal, the patient showed a marked improvement without serious side effects. INF-g was suspended based on his clinical improvement (mainly the disappearance of high fever and amelioration of analytics). Thus, the duration of INF-g therapy was shorter (3 months) than that described in cases of ICL. The use of INF-g as adjuvant therapy has not previously been described in the treatment of *M. chimaera* IE. Its beneficial effect in our patient could be due to an improvement in cellular immune response, and we consider that it could be useful in future cases.

On the other hand, the duration of the antibiotic treatment in *M. chimaera* IE is not well established (minimum 12 months).<sup>1</sup> In this case, FDG PET/CT findings were used, not only for its role in diagnosing prosthetic valve IE,<sup>19,20</sup> but also to guide decision making with respect to determining when to cease antibiotic treatment.

A further FDG PET/CT was performed 3 months post-surgery and was repeated before stopping antibiotics. The absence of uptake in the new prosthetic aortic valve supported the diagnosis that the

new prosthesis had not been infected, and the absence of uptake in the thigh suggested that the suspected mycobacterial abscess had been resolved. Subsequent necropsy findings confirmed that the *M. chimaera* infection had been successfully treated.

In conclusion, diagnosis of *M. chimaera* IE is difficult and requires a high index of clinical suspicion. Controlling the infection is even more difficult. INF-g adjuvant to surgery and antibiotic therapy could be useful to achieve this goal. Given that the appropriate duration of antibiotics is unknown, FDG PET/CT could be a valuable tool to determine when antibiotic therapy should be stopped.

## Supplementary material

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

**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.

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