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GRAND ROUND
Cardiovascular imaging

Role of molecular imaging in the diagnosis of prosthetic aortic valve endocarditis by *Bacillus licheniformis*: a case report

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Background Infective endocarditis is a challenging diagnosis that usually requires cardiovascular image confirmation as part of the approach. ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) is an imaging technique more sensible for the diagnosis of prosthetic valve endocarditis (PVE) when echocardiography is inconclusive.

Case summary We present the case of a 35-year-old man who had a previous Bentall–De Bono procedure 4 years prior that included biological, national institute of cardiology (INC)-type, locally manufactured aortic valve replacement and woven Dacron tube graft implantation in the ascending aorta. He was admitted because of dyspnoea, oedema, fever, and syncope. A complete auriculoventricular blockade was diagnosed, requiring cardiac pacing. Also, infective endocarditis (IE) was suspected. Blood cultures showed the isolation of *Bacillus licheniformis*. Transthoracic echocardiography, transoesophageal echocardiography, and CT angiography were inconclusive for IE. Treatment was initiated with intravenous (IV) antibiotic therapy, and an extensive protocol for IE, including molecular imaging modalities, was ordered. ^{99m}Tc-Ubiquicidin scintigraphy was acquired without abnormal findings. Images of ^{18}F-FDG-PET/CT revealed abnormally intense heterogeneous uptake in the prosthetic aortic annulus in a classic pattern. Applying the modified 2015 Duke criteria for PET/CT, PVE was confirmed.

Discussion Although the other imaging modalities were negative, the high clinical suspicion made it mandatory to continue the study protocol, remarking on the utility of ^{18}F-FDG-PET/CT on patients categorized as having 'possible' endocarditis, as in our patient.

Keywords Infective endocarditis • Molecular imaging • ^{18}F-FDG-PET/CT • Prosthetic valve • Case report

ESC curriculum 2.1 Imaging modalities • 2.5 Nuclear techniques • 4.11 Endocarditis

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Learning points

- In patients with an inconclusive diagnosis of prosthetic valve endocarditis despite other imaging methods and with a high grade of clinical suspicion, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) should be considered as the next option.
- The ^{18}F-FDG-PET/CT provides higher diagnostic accuracy for infectious endocarditis than modified Duke criteria or even a combination of both diagnostic methods.
- The FDG-PET/CT offers an alternative for detecting the infectious process, its exact location and extension, and even assessing the response to the established treatment.

Primary specialties involved other than cardiology

Nuclear medicine, infectious disease, and echocardiography.

Introduction

Infective endocarditis (IE) refers to infection of the endocardial surface of the heart; it usually involves one or more heart valves or an intracardiac device. The diagnosis of IE may be difficult given its non-specific symptoms. Modified Duke criteria (DC) are the accepted criteria for the diagnosis of IE, but in some scenarios, such as in the case of prosthetic valve endocarditis (PVE), the diagnosis could be more challenging. Transthoracic echocardiography (TTE) in this situation has a low sensitivity; hence, a transoesophageal echocardiogram (TEE) is frequently performed, increasing the sensitivity to 70–80%; however, even with these studies, the diagnosis is not clear in some cases.

In 2013, Saby *et al.*[1] evaluated the impact of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) as a major Duke criterion in 72 patients with a prosthetic valve. They found that patients with possible endocarditis benefited the most, allowing for reclassification as a 'definite diagnosis' of PVE. This approach had a significant impact on therapeutic strategies and clinical outcomes. Recent studies support this evidence and confirm that ^{18}F-FDG-PET/CT represents a valuable diagnostic tool that could be proposed for challenging IE cases with significant differences between DC and clinical suspicion degree.[2]

All this evidence allowed the European Society of Cardiology (ESC) guidelines for the management of IE to include the use of ^{18}F-FDG-PET/CT in the diagnostic workup of PVE for the first time in 2015.[3]

We present a clinical case of a patient with possible PVE in which molecular imaging played an essential role in the diagnosis.

Summary figure

Four years before admission	Bentall–De Bono surgery was performed due to severe aortic regurgitation secondary to a bicuspid aortic valve.
During the last month before admission	Oedema of the lower extremities, dyspnoea, fever, and diaphoresis.
One week before admission	Three syncopal episodes, the last of which was accompanied by Stoke–Adams syndrome.
At the coronary care unit	He was found feverish with a holosystolic murmur in the aortic area.
During hospitalization	Third-degree atrioventricular block and temporary pacemaker implantation, with clinical improvement.
During hospitalization	Positive blood cultures and clinical suspicion of *Bacillus licheniformis* infective endocarditis. Empiric antibiotic treatment was started. TTE showed an increase in aortic blood velocity, without evidence of endocarditis. Permanent pacemaker implantation.
During hospitalization	TEE, computed tomography angiography (CTA), and scintigraphy were obtained with no positive results suggesting endocarditis.
During hospitalization	^{18}F-FDG-PET/CT was obtained with a positive result. A definitive diagnosis of infective endocarditis was established.
After 30 days	The antibiotic regimen was enhanced with good clinical and biochemical evolution and hospital discharge.
Two months after hospital discharge	Follow-up TTE showed normalization of speed through the aortic valve prosthesis.

Case presentation

We present a 35-year-old male with a previous diagnosis of systemic lupus erythematosus and lupus nephritis. Four years ago, he developed severe aortic regurgitation secondary to a bicuspid aortic valve, which required Bentall–De Bono surgery that included the placement of a woven Dacron tube graft of 28 mm in the ascending aorta plus a biological 26 mm INC-type locally manufactured aortic valve replacement. One month before admission, he began with swelling of the lower extremities and dyspnoea; a few days later, fever and diaphoresis were added. One week before his admission, he had three episodes of syncope, the last one accompanied by Stoke–Adams syndrome, which is why he came to our emergency department.

On arrival, he was found to have a temperature of 99.8°F (37.7°C) and a heart rate of 40 b.p.m. Physical examination revealed an intense Grade III/IV holosystolic murmur in the aortic area. In laboratory studies, 17.3×10^9/L leucocytes (normal range $< 9.79 \times 10^9$/L), 14.6×10^9/L neutrophils (normal range $< 6.48 \times 10^9$/L), 31 mg/L C-reactive protein (normal range < 5 mg/L), 8.180 µg/mL D-dimer (normal range < 0.24 µg/mL), 2449 pg/mL N-terminal (NT)-prohormone BNP (normal range = 0 pg/mL), and 40.7 ng/L high-sensitivity T troponin (normal

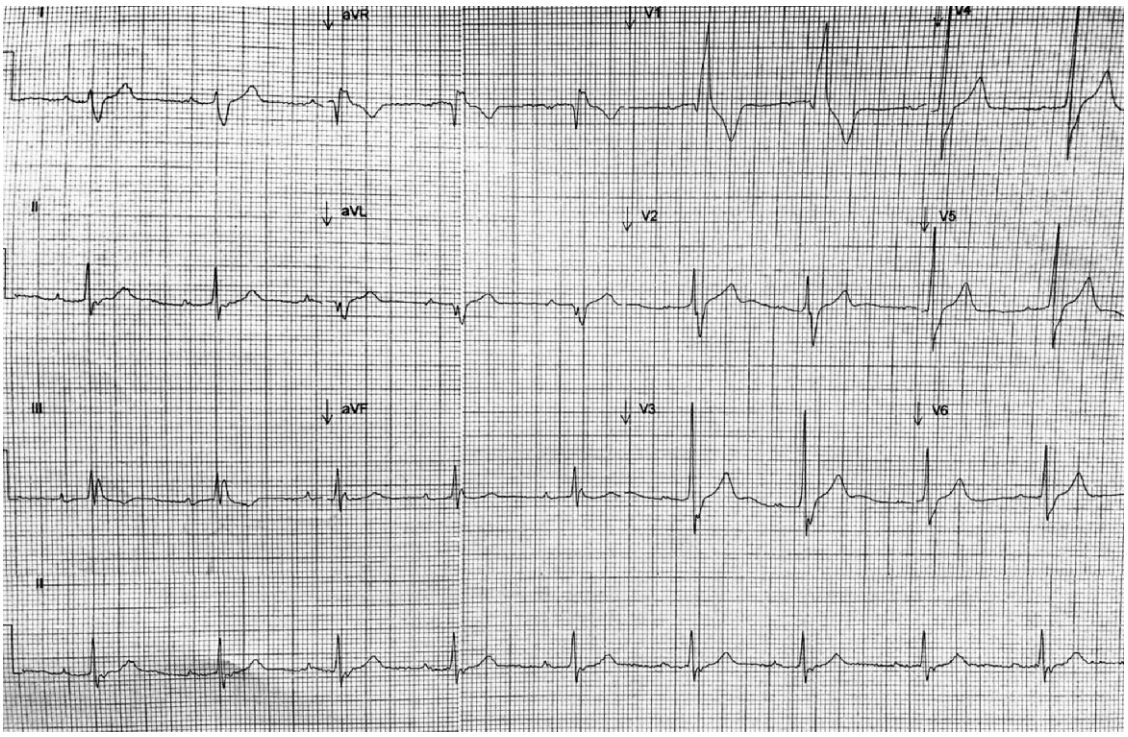

Figure 1 Basal electrocardiogram. Sinus rhythm with complete right bundle branch block and first-degree atrioventricular block.

range < 14) were found. The initial electrocardiogram showed a sinus rhythm with a complete right bundle branch block and a first-degree atrioventricular block (*Figure 1*).

Due to symptoms and biochemical findings, he was admitted to the coronary care unit to rule out prosthetic valve dysfunction and possible IE. Two days later, he developed a third-degree atrioventricular block requiring a temporary pacemaker, resulting in a notable reduction of symptoms without impact on fever or inflammatory biomarkers. Seven days later, a permanent pacemaker was placed. Meanwhile, TTE was performed, showing an aortic valve prosthesis with an increased velocity gradient (maximum velocity gradient of 4 m/s and a median gradient of 37 mmHg) with a mild central regurgitation flow without paravalvular leaks. No evidence of an aortic root abscess or vegetations (*Figure 2A*; see Supplementary material online, *Videos S1 and S2*). The left ventricular ejection fraction (LVEF) was preserved (68%). The mitral and tricuspid valves had mild insufficiencies. A complimentary TEE was obtained, which did not find suggestive images of IE (see Supplementary material online, *Videos S3–S5*). Continuing the approach for IE, CTA was performed without evidence of perivalvular complications, but an infarction on the right kidney was found, which was considered a probable embolic phenomenon (*Figure 3*). ^{99m}Tc-Ubiquicidin scintigraphy was performed without evidence of abnormal uptake (*Figure 4*). The patient continued having feverish episodes, and *B. licheniformis* was found in two of the four serial blood cultures; an evaluation by the infectious disease department led to the decision to start empiric antibiotic treatment with IV vancomycin within 48 h from admission.

Until that moment, the modified DC categorized the patient as 'possible IE' with four minor criteria (positive blood culture but not meeting major criteria, fever, presence of embolic phenomena, and a predisposing condition). However, no imaging study could evidence the infection (TTE, TEE, CTA, or ^{99m}Tc-ubiquicidin scintigraphy); therefore, following the 2015 ESC guideline recommendation, it was decided to complement with ^{18}F-FDG-PET/CT, a non-invasive nuclear imaging technique, as part of the diagnostic protocol.

The patient had adequate preparation 24 h before the study with a low-carbohydrate, high-fat, and protein diet, avoiding IV glucose solutions, and prolonged 15-h fasting. Since the patient had different probable sites of infection (Bentall–De Bono surgery, a valve prosthesis, and a pacemaker), a whole-body PET study was acquired according to the protocol for a patient with a fever of unknown origin. Images were reconstructed with and without attenuation correction. An additional dedicated cerebral bed was acquired, looking for septic emboli.

The ^{18}F-FDG images showed abnormally intense heterogeneous uptake in the prosthetic aortic annulus with focal uptake around valve sutures and periprosthetic extension to the ascending aorta graft with maximum standardized uptake value (SUV_{max}) of 8.2 (*Figures 5–7*). The pattern was persistent on non–attenuation-corrected (NAC) images, ruling out overcorrection artefacts. Non-enchanted CT images showed a poorly delimited perivalvular soft tissue lesion.

With these findings, and according to the 2015 ESC guidelines, we considered ^{18}F-FDG-PET/CT a major criterion of the modified DC for IE diagnosis, letting us reclassify the patient towards a 'definitive IE' diagnosis due to *B. licheniformis*.

After antimicrobial susceptibility testing, the organism proved susceptible to cephalothin, gentamicin, clindamycin, vancomycin, and trimethoprim–sulfamethoxazole. Based on susceptibilities, IV antibiotic therapy was adjusted with IV trimethoprim–sulfamethoxazole.

The case was discussed, and it was concluded that surgical treatment should not be performed due to the high surgical risk and the fact that the isolated pathogen responsible for the IE had a slow growth rate and there was no evidence of vegetation or perivalvular compromise; additionally, the fever and inflammatory biomarkers had decreased. Likewise, the patient's symptoms improved significantly after the cardiac peacemaker was implanted, which suggested that clinical decompensation at presentation was secondary to a degree of

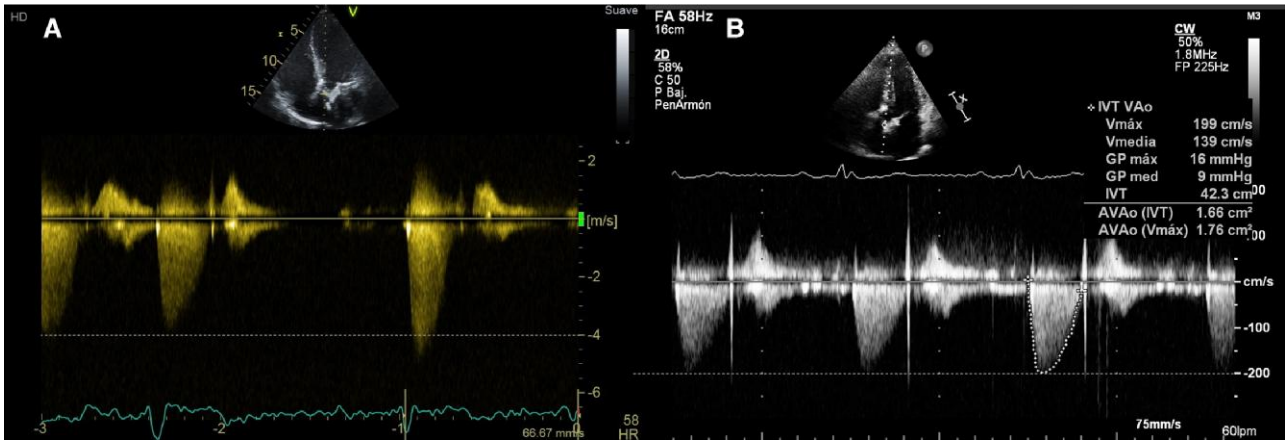

Figure 2 Transthoracic echocardiogram. (*A*) Initial transthoracic echocardiography: continuous-wave Doppler velocity with an observed increase in aortic blood velocity (maximum velocity gradient of 4 m/s and median gradient of 37 mmHg) without evidence of vegetations suggesting endocarditis. (*B*) Follow-up transthoracic echocardiography 2 months after discharge. Imaging showed improvement in aortic blood velocity after antibiotic treatment (maximum velocity gradient of 1.9 m/s, median gradient of 8 mmHg).

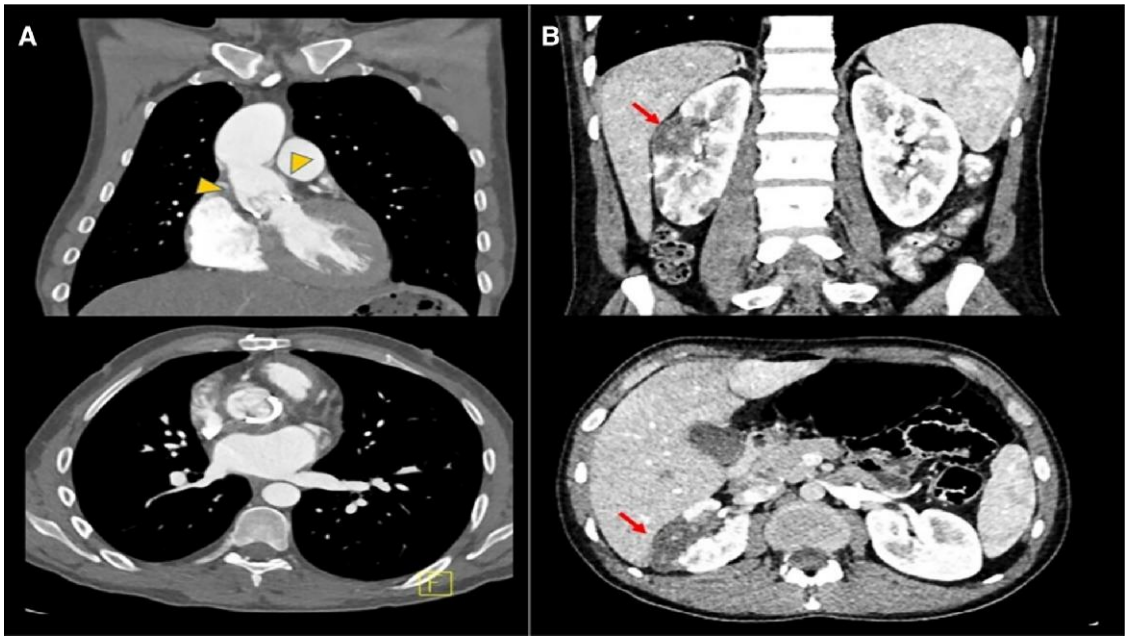

Figure 3 Computed tomography angiography. (*A*) Ascending aorta with post-surgical changes by Bentall–De Bono with biological prosthesis and woven Dacron graft, associated with hyperdense surgical material (triangles). There's no evidence of suggestive findings of mediastinitis, collections, or infectious process. (*B*) Right kidney with suggestive images of infarctions (red arrows).

atrioventricular block. With that evidence, it was decided to continue with IV antibiotics over 4 weeks.

After remission of fever, decreased inflammatory response, and negative control blood cultures, the patient was discharged in good clinical condition with the indication to continue on antibiotics for two more weeks.

Two months later, a follow-up TTE was performed. The patient was in good clinical condition, and the imaging showed improvement in increased velocity gradient through the aortic valve prosthesis (maximum velocity gradient 1.9 m/s, median gradient 8 mmHg), which confirms the response to conservative treatment (*Figure 2B*; see Supplementary material online, *Video S6*).

Discussion

The ^{18}F-FDG is a radiopharmaceutical molecule with overexpression of specific glucose receptors in various pathologies in hibernating myocardium (GLUT4 receptors) and inflammatory cells (GLUT1 and GLUT3

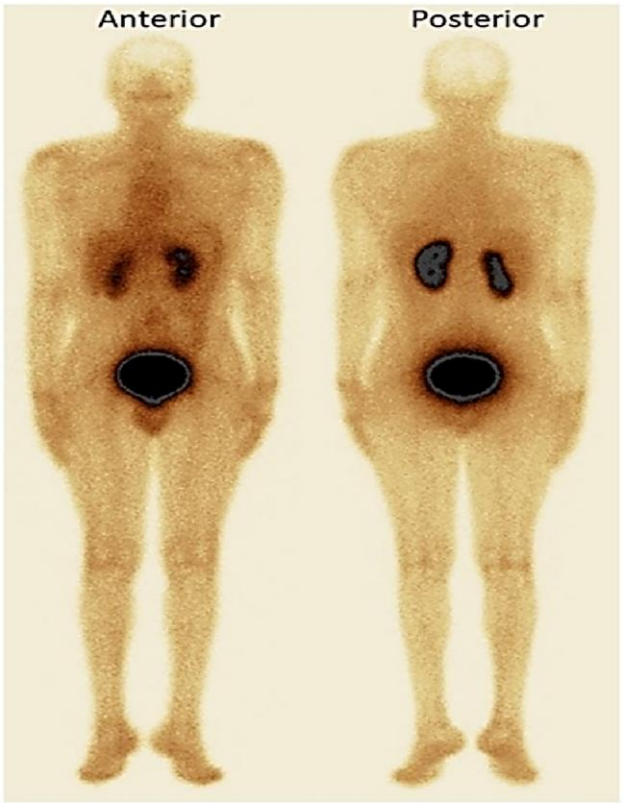

Figure 4 ^{99m}Tc-Ubiquicidin scintigraphy. Normal biodistribution. There is no evidence of infection foci.

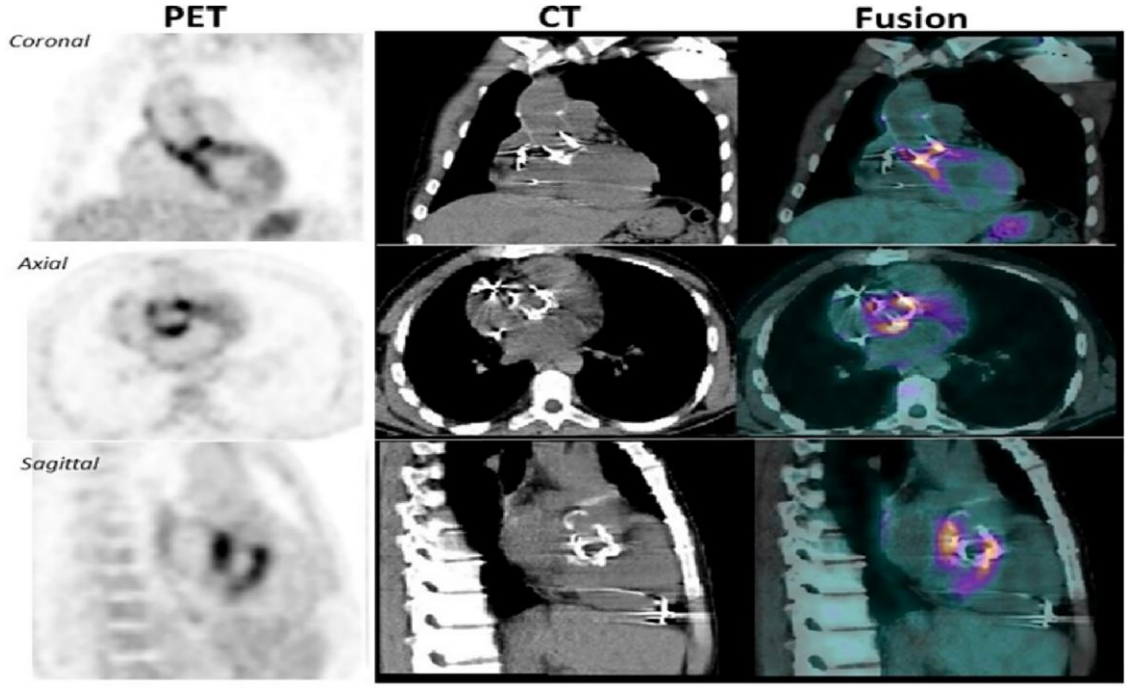

Figure 5 ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography showed abnormal intense heterogeneous uptake in the prosthetic aortic annulus with focal uptake around valve sutures and periprosthetic extension to the ascending aorta graft with maximum standardized uptake value (SUV_{max}) of 8.2.

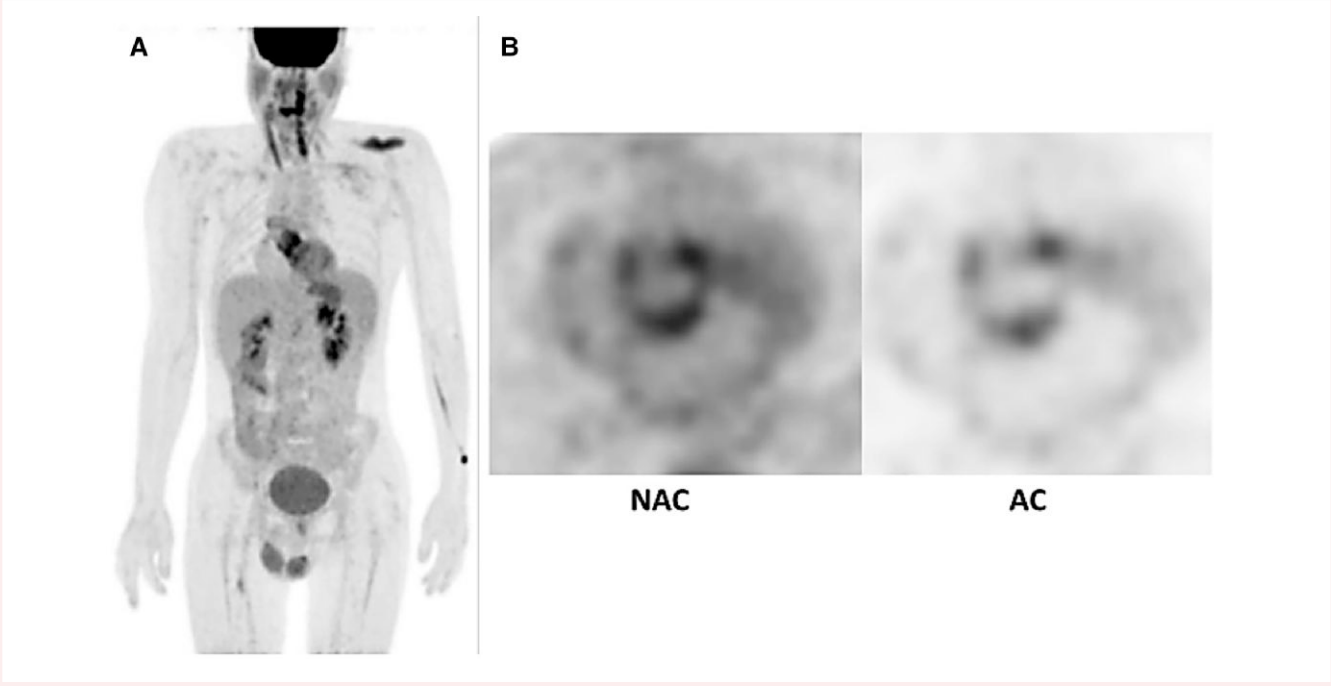

Figure 6 ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography. (*A*) Maximum intensity projection showing abnormal distribution because of an intense heterogeneous uptake in the midline of the thorax and the shoulder. (*B*) Axial images in the aortic plane showing the persistence of the uptake in both images with and without attenuation correction.

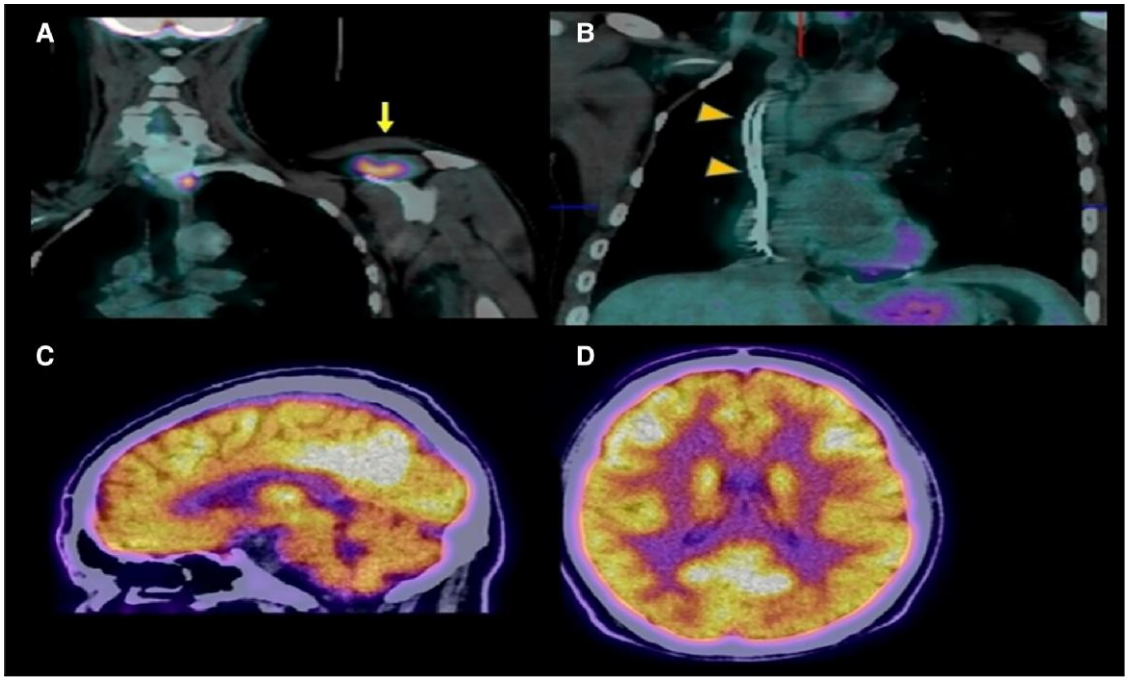

Figure 7 ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography fusion images. (*A*) Abnormal uptake that corresponds to muscle contracture (arrow). (*B*) Pacemaker lines without evidence of any uptake (triangles). (*C*, *D*) Normal cerebral biodistribution of ^{18}F-fluorodeoxyglucose.

receptors). Inhibiting physiological myocardial uptake with a diet and appropriate measures without affecting GLUT overexpression gives ^{18}F-FDG-PET/CT a significant advantage in detecting multiple infected processes such as endocarditis, endarteritis, and intracardiac device infections.[4]

According to the ESC guidelines for IE (ESC 2015), modified DC are implemented for establishing clinical suspicion degree from 'possible' to 'rejected' endocarditis, despite a persistently high level of clinical suspicion. In this clinical case, positive blood cultures for *B. licheniformis* were the only microbiological DC since TTE and TEE were both negative for endocarditis. As a result, our patient was initially diagnosed with possible IE.

Pretet *et al.* compared the diagnostic utility of ^{18}F-FDG-PET/CT vs. DC specifically in the group of patients who were classified as 'possible'/'rejected' (excluding those who were 'definite' IE) with high clinical suspicion, such as in our patient. It was demonstrated that ^{18}F-FDG-PET/CT performed significantly better than DC ($P = 0.003$) and a combination of both ($P = 0.001$) for IE diagnosis. This imaging method showed high sensitivity (78%), specificity (100%), positive predictive value (100%), negative predictive value (85%), and global accuracy (90%).

Moreover, the diagnostic performance of ^{18}F-FDG-PET/CT could even be improved when acquired simultaneously with a CTA, yielding even better diagnostic performance values than non-enhanced PET/CT (91, 90.6, 92.8, and 88.3% vs. 86.4, 87.5, 90.2, and 82.9%, respectively). This might substantially reduce the rate of doubtful cases from 20 to 8% ($P < 0.001$).[4]

The preparation of this study is essential to increasing its sensitivity. It consists of a 24- to 72-h low-carbohydrate/high-fat and protein diet to modify the metabolic substrate physiology of the myocardium, diverting toward fatty acids instead of glucose. Prolonged fasting (12 h minimum) is another mandatory recommendation. In some centres, 50 IU/kg heparin is applied 15 min before ^{18}F-FDG administration, to take advantage of its lipolytic activity and increase the production of fatty acids as a substrate for myocardial cells.[5]

The ^{18}F-FDG-PET/CT allows classifying the results as positive for active infection when there is evidence of intense heterogeneous hypermetabolism related to the prosthetic material; negative for active infection when metabolic activity is absent; or doubtful when there is a homogeneous low-intensity uptake, especially in recently operated patients.[6]

Pizzi *et al.*[7] have described some differences in uptake characteristics and patterns between inflammation and infection: (i) inflammation has a mild SUV_{max} intensity and homogenous/diffuse distribution, mainly around the sutures, accompanied by minimal or no abnormal findings on CTA and (2) infection has an intense SUV_{max} and heterogeneous/focal distribution located on prosthetic and aortic grafts with tube and peritube uptake greater than sutures, usually accompanied by CTA changes (leaflets, vegetation, pseudoaneurysms, abscesses, and collections).

SPECT/CT with ^{99m}Tc radiotracers (ubiquicidin or ciprofloxacin) is sometimes preferred because they are more available, provide better image quality, and lower patients' radiation burden.[8] The use of radiolabelled white blood cells (WBC) is more specific for detecting IE and infectious foci than ^{18}F-FDG-PET/CT. It uses autologous radiolabelled leucocytes after radiolabelling with ^{111}In-oxine or ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO). It should be preferred in all situations that require enhanced specificity.[3] The disadvantages of scintigraphy with radiolabelled WBC are the requirement of blood handling for radiopharmaceutical preparation, the long duration of the procedure, and a lower spatial resolution.[9] In our patient, a UBI scan was performed because it was an immediately available study, while the radiolabelled WBC was more complex, and there was no availability of the material.

Another added value of using these molecular imaging techniques is that whole-body studies are acquired, making it possible to detect peripheral embolic and metastatic infectious events. The ^{18}F-FDG-PET/CT limitations are represented by the localization of septic emboli in the brain due to the high physiological uptake and due to poor study quality in patients with inadequate preparation, where the intense physiological myocardial uptake does not allow a suitable assessment of the site of interest (valves, grafts).[3] Another limitation of ^{18}F-FDG is in patients with cardiac surgery 3 months prior, because false positives may occur due to normal post-surgical inflammation.[7]

According to the 2015 ESC guidelines, radiolabelled leucocyte scintigraphy and ^{18}F-FDG-PET/CT imaging may be considered as an additional tool in patients with suspected cardiac device–related IE, positive blood cultures, and negative echocardiography (Class IIb, level of evidence C). Furthermore, there is a promising role for ^{18}F-FDG-PET/CT in patients with established IE, in whom it could be employed to monitor response to antimicrobial treatment.[3]

The FDG-PET/CT has already been used to monitor the effect of IE treatment and guide therapeutic decision-making in several conditions, including oncological diseases, invasive fungal infections, tuberculosis, spondylodiscitis, and aortic graft infections. However, for IE, sufficient data are not available at this time to make a general recommendation.[10]

Because there are no current formal recommendations on repeating the PET scan during follow-up to demonstrate that the infection had indeed cleared, in addition to the resource limitations in our hospital and because our patient presented clinical and echocardiographic improvement, it was decided not to repeat the study.

It is worth highlighting the importance of this clinical case since the isolated bacterium *B. licheniformis* is extremely unusual as a cause of endocarditis. This patient suffered from generalized lupus erythematosus and was treated with mycophenolate as immunosuppressive therapy due to underlying lupus nephritis. On the other hand, *B. licheniformis* is a bacterium found in soil and bird feathers. Our patient currently works as a farmer, which might be an important factor for exposure. Santini *et al.*[11] published the first case of PVE due to *B. licheniformis* in a patient who required surgery as definitive treatment; however, our patient had a favourable evolution with IV antibiotic therapy.

Conclusions

The ^{18}F-FDG-PET/CT represents a valuable diagnostic tool that could be proposed for challenging IE cases. It offers an alternative for detecting the infectious process, its exact location, its extension, and even assessing the response to the established treatment. It should be considered the next option for patients with an inconclusive diagnosis.

This case shows a challenging diagnosis of IE caused by an extremely rare bacterium, in which a definite diagnosis could be reached following the 2015 ESC guidelines with the use of new imaging modalities.

Lead author biography

Isabel Carvajal Juarez was born in Mexico and graduated from the Autonomous University of Nuevo Leon in Monterrey with the degree of Doctor of Medicine. She post-graduated from the National Institute of Respiratory Diseases Ismael Cosio Villegas in the specialty of Nuclear Medicine and Molecular Imaging and achieved the specialty of Nuclear Cardiology at the National Institute of Cardiology, Ignacio Chavez. Her expertise is focused on Nuclear Cardiology with special knowledge of PET/CT, and she has dedicated an important part of her practice to clinical investigation and publication.

Supplementary material

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

Consent: The authors confirm that written consent for submission and publication of this case report including the images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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