

Recurrent strokes in an occult case of recurrent *Cutibacterium acnes* prosthetic valve infective endocarditis: a case report

Charles Fry ^{1†}, Christopher P. Primus ^{1,2,*†}, Robert Serafino-Wani ¹, and Simon Woldman ¹

¹Barts Heart Centre, St Bartholomew's Hospital, W Smithfield, London EC1A 7BE, UK; and ²William Harvey Research Institute, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK

Received 25 August 2020; first decision 1 October 2020; accepted 9 April 2021

Background

Infective endocarditis (IE) is a known but uncommon cause of cardioembolic stroke and there are rare but recognized cases of IE without an inflammatory response. *Cutibacterium acnes* is an increasingly recognized source of invasive infections, including IE, but diagnosis is challenging due to its low virulence and fastidious nature.

Case summary

A 47-year-old man presented with a multi-focal stroke suggestive of a cardioembolic source. Outpatient transoesophageal echocardiography (TOE) was concerning for vegetation or thrombus associated with his previous mitral valve repair. He remained clinically well, with no evidence of an inflammatory response and sterile blood cultures. Computed tomography–positron emission tomography (CT–PET) corroborated the TOE findings, however, given the atypical presentation, he was treated for valvular thrombus. Following discharge, he quickly re-presented with further embolic phenomena and underwent emergency mitral valve replacement. Intraoperative findings were consistent with prosthetic valve IE (PVE) and a 6-week course of antibiotics commenced. *C. acnes* was identified on molecular testing. Eighteen months later, he re-presented with further neurological symptoms. Early TOE and CT–PET were consistent with IE. Blood cultures grew *C. acnes* after prolonged incubation. Given the absence of surgical indications, he was managed medically, and the vegetation resolved without valvular dysfunction. He continues to be followed up in an outpatient setting.

Discussion

In patients presenting with multi-territory stroke, IE should be considered despite sterile blood cultures and absent inflammatory response. *C. acnes* is an increasingly recognized cause of PVE in this context, often requiring surgical intervention. A high index of suspicion and collaboration with an Endocarditis Team is therefore essential to diagnose and treat.

Keywords

Case report • Infective endocarditis • *Cutibacterium acnes* (*Propionibacterium acnes*) • Prosthetic valve endocarditis • Positron emission tomography • PET • Transoesophageal echocardiography • Endocarditis Team

* Corresponding author. Tel: +44 (0)20 3765 8711, Email: christopher.primus@nhs.net

†Dr Fry and Dr Primus are joint first authors

Handling Editor: Alberto Bouzas-Mosquera

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Compliance Editor: Matteo Parollo

Supplementary Material Editor: Aiste Monika Jakstaite

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Learning points

- In patients presenting with multi-territory stroke, infective endocarditis (IE) should always be considered even if other clinical signs are absent.
- A lack of inflammatory response, including normal white cell count and C-reactive protein, does not exclude IE.
- *Cutibacterium acnes* positive blood cultures are often disregarded as a contaminant but is a known cause of IE, is found more commonly in prosthetic valves, and requires prolonged antibiotic treatment.
- Long-term psychological support should be considered in patients with IE.

Introduction

Infective endocarditis (IE) is a known but uncommon cause of cardioembolic stroke.¹ In the initial stages, raised inflammatory markers and/or positive blood cultures often prompt diagnostic echocardiography.² However, in the absence of these features, recognizing IE is challenging.³ *Cutibacterium acnes* (formerly *Propionibacterium*) is an anaerobic Gram-positive bacillus that is a normal human skin commensal.⁴ Isolation of *C. acnes* on blood culture is commonly disregarded as a skin contaminant,⁵ but is an increasingly recognized cause of invasive infection, including IE.⁴ If positive blood cultures are disregarded as contaminants, then the diagnosis of IE by modified Duke Criteria (mDC) is easily missed.² Collectively, these factors often make the diagnosis of IE challenging, especially when presenting with stroke.

Timeline

Case presentation

In October 2016, a 47-year-old man presenting with stroke syndrome was diagnosed with right frontoparietal infarct and multi-territory foci on magnetic resonance imaging-brain. Past medical history was notable for mitral valve (MV) repair in 2009 and current medications included Clopidogrel 75 mg and Omeprazole 20 mg once daily. There was no history of constitutional symptoms, and screening investigations for a central embolic source were normal. Outpatient transoesophageal echocardiography (TOE) was therefore planned.

TOE in December 2016 showed a strand-like structure (<10 mm) associated with a competent MV repair (*Figure 1, Video 1*); he was admitted to differentiate IE from thrombus. He was afebrile with no significant findings on examination and normal inflammatory markers [white cell count (WCC) 7.3×10^9 g/L and high sensitivity C-reactive protein (CRP) <5 mg/L]. Four sets of peripheral blood cultures were sterile. Serology for Coxiella, Bartonella, Brucella, Syphilis, and an autoimmune screen was negative; whole blood polymerase chain

2009

Mitral valve (MV) repair for severe mitral regurgitation

Episode 1

October 2016	Right frontoparietal infarct with multi-territory foci; full neurological recovery. No inflammatory response: white cell count (WCC) 7.1×10^9 /L and C-reactive protein (CRP) <5 mg/L. Magnetic Resonance Imaging-brain suggests possible cardioembolic source. Outpatient transoesophageal echocardiography (TOE) arranged.
8 December 2016	TOE concerning for MV vegetation with normal valve function. Apyrexial. Inflammatory markers normal: WCC 7.3×10^9 /L and CRP <5 mg/L; blood cultures negative; positron emission tomography (PET) concerning for prosthetic valve infective endocarditis (IE) (PVE). Patient treated for possible blood culture negative infective endocarditis by the Endocarditis Team using modified Duke Criteria (mDC). Clinical decision to treat as thrombus at 2 weeks: negative blood cultures, consistently normal inflammatory markers, no pyrexia.
26 December 2016	Left parietal cerebral infarct with full recovery. Emergency MV replacement (MVR): intraoperative findings consistent with IE. Fully sensitive growth of <i>Streptococcus sanguinis</i> on enrichment culture; 16S molecular testing positive for <i>Cutibacterium acnes</i> bacterial DNA. 6-weeks post-operative antibiotics.
31 July 2018	Dizzy spells and high-grade atrioventricular block diagnosed. Pacemaker implant planned.
Episode 2	
9 August 2018	Right occipital infarct, presenting as transient ischaemic attack. Afebrile, WCC 6.9×10^9 /L and CRP 7 mg/L. Small MVR vegetation on TOE with normal valve function.
10 August 2018	Blood cultures positive for <i>C. acnes</i> and 6 weeks of antibiotics commenced (definite IE by mDC). Systemically well throughout admission.
16 August 2018	PET concerning for PVE
21 August 2018	Repeat TOE shows vegetation has grown to 1.1×0.6 cm, with trivial paravalvular regurgitation. Decision for medical management of PVE.
September–October 2018	Fortnightly TOE shows no progressive valve dysfunction and ultimate resolution of vegetation.
17 October 2018	Discharged on 6-month course of Amoxicillin.
October 2018–April 2021	Close follow-up with no recurrence of symptoms, inflammatory markers unchanged, and no change in TOE appearances. Single episode of dizziness without objective evidence of arrhythmia, recurrent IE, or stroke.

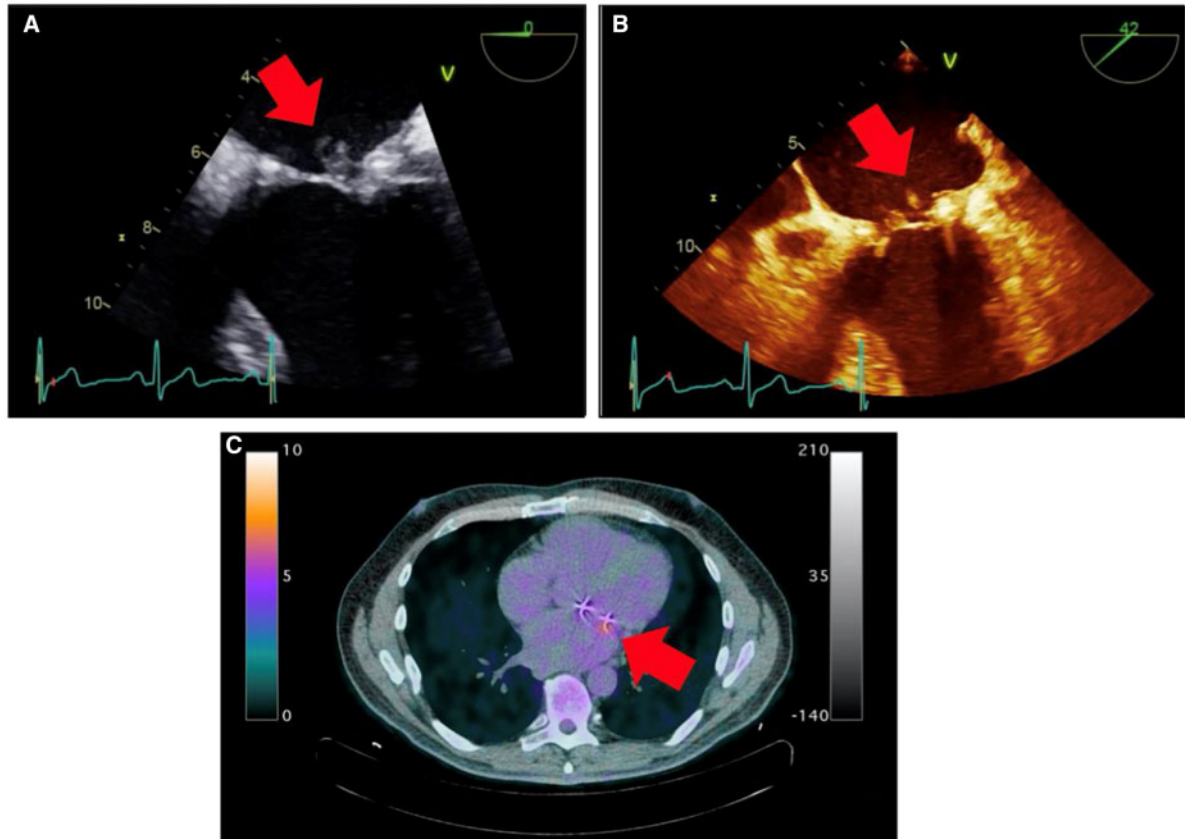
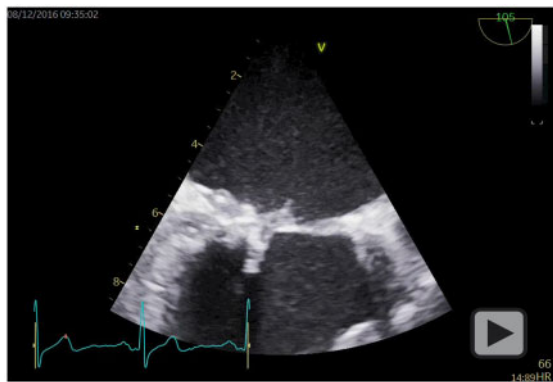


Figure 1 Transoesophageal echocardiography and computed tomography–positron emission tomography findings, December 2016. Panels A and B highlight the echolucent mass associated with the posterior mitral valve annulus on TOE. Cine imaging (Video 1) shows the mass moving in and out of plane, independent of the valve leaflets. Panel C depicts a transaxial cCT-PET fusion image following successful suppression of myocardial uptake with a carbohydrate-restricted diet + heparin bolus at the time of image acquisition in the same patient. There is focal tracer avidity localizing to the posterior mitral valve annulus associated with the prosthetic ring. These findings were interpreted as concerning for IE.



Video 1 TOE demonstrates a <10mm strand-like structure associated with a competent mitral valve repair. The differential was vegetation versus thrombus. The Endocarditis Team were concerned about IE despite a lack of positive cultures and elevated inflammatory markers given the appearances.

reaction (PCR) is not performed in our Trust due to low sensitivity.⁶ 18F-fluorodeoxyglucose positron emission tomography–computed tomography (CT-PET) showed focal posterior mitral annular uptake, typical for IE (Figure 1). IE was possible by mDC [one major plus two minor; possible vegetation on TOE (major), MV repair as a predisposing risk factor (minor) and multi-territory stroke as embolic phenomena (minor)] and so the Endocarditis Team recommended repeat TOE in 2 weeks, anticoagulation and Flucloxacillin, Benzylpenicillin, and Gentamicin for culture negative prosthetic valve IE (PVE). After 2 weeks however, the clinical team noted the negative blood cultures, persistently normal inflammatory markers and apyrexia; antibiotics were stopped and the patient anticoagulated with Apixaban 5 mg twice daily for valve thrombus.

Four days later, he re-presented with self-resolving objective facial and limb weakness. He remained apyrexial with normal inflammatory markers (WCC 7.7×10^9 g/L and CRP <5 mg/L). His mDC score was unchanged, but given recurrent embolic phenomena, inspection of the MV repair and resection of the underlying cause was mandated.

Intraoperative findings were of an irregular mass attached to the posterior mitral annuloplasty ring. There was regional dehiscence

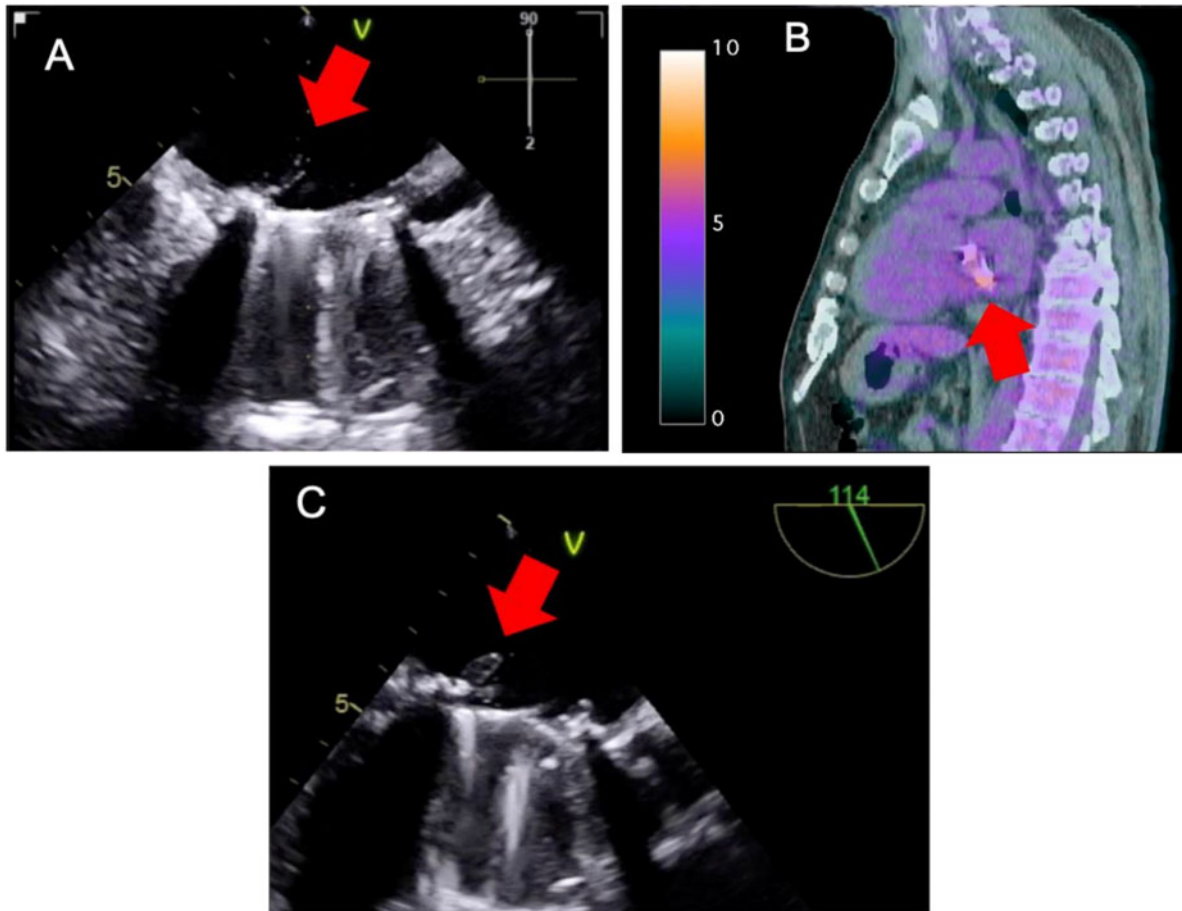
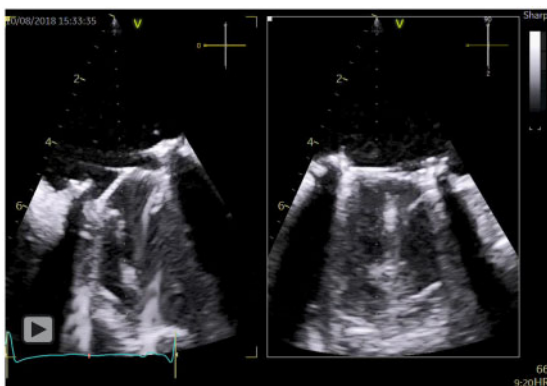


Figure 2 Transoesophageal echocardiography and computed tomography–positron emission tomography findings, August 2018. Panel A is concerning for a strand-like structure associated with the posterior mitral valve replacement annulus, without valve dysfunction. Panel B, 1 week later, depicts a sagittal CT-PET fusion image following myocardial suppression (as described above) highlighting increased focal tracer uptake in the posterior mitral valve replacement. Panel C depicts progression of TOE findings to a 1.1×0.6 cm vegetation consistent with IE. This resolved entirely over the course of his patient admission.



Video 2 At presentation, there was a 10mm indeterminate lesion associated with posterior MVR, with normal valve function. This prompted treatment for IE, which was possible by mDC.



Video 3 After 1 week of treatment, TOE was repeated and showed progression of the indeterminate lesion to a 11×6 mm mobile vegetation attached to the posterior annulus. There was good excursion of the disc and only trivial paravalvular regurgitation.

with areas of necrotic tissue suggestive of PVE. A 29 mm Carbomedics valve was implanted. Direct valve culture grew fully sensitive *Streptococcus sanguinis* on enrichment and was considered significant. *Cutibacterium acnes* ribosomal DNA (rDNA) was identified on 16S molecular testing and deemed a contaminant. Given the intraoperative findings, the previous antibiotics were recommenced for 2 weeks followed by 4 weeks of intravenous outpatient Ceftriaxone monotherapy.

In August 2018, 18 months later, he presented to his local hospital complaining of post-syncopal right frontal headache, diplopia, and transient left arm paraesthesia; stroke was confirmed on CT-Head. Since discharge, he had been diagnosed with presyncope secondary to 2:1 and 3:1 atrioventricular block and had been listed for pacemaker implantation.

He was afebrile, had no significant findings on examination and near normal inflammatory markers (WCC 6.9×10^9 g/L and CRP 7 mg/L), and a normal electrocardiogram. His medications included: Warfarin [target INR (international normalized ratio) 2.5–3.5], Omeprazole 40 mg, Candesartan 4 mg, Atorvastatin 40 mg once daily. Given his previous history, he was transferred for urgent imaging at Barts Heart Centre. TOE was concerning for a small indeterminate lesion (10 mm) associated with the posterior MV replacement (MVR), with normal valve function (Figure 2, Video 2). IE was initially possible by mDC [one major plus two minor; possible vegetation on TOE (major), MVR and previous PVE as predisposing risk factors (minor) and multi-territory stroke as embolic phenomena (minor)], but prolonged incubation of the blood cultures grew fully sensitive *C. acnes* (2/6 bottles), and was considered significant given the previously disregarded 16S findings. Focal avidity of the posterior MVR was demonstrated on repeat PET-CT (Figure 2). Interval TOE at 1 week showed progression of the suspicious lesion to an 11×6 mm mobile vegetation attached to the posterior annulus, with good excursion of the disc and only trivial paravalvular regurgitation (Figure 2, Video 3). The Endocarditis Team opted to manage the case medically with a 6-week course of Benzylpenicillin and Rifampicin. Fortnightly TOE was planned to monitor progress of the vegetation, given absence of elevated biomarkers. There were no surgical indications, and redo surgery was deemed high-risk given two previous sternotomies.

Sequential TOE showed progressive reduction and ultimately resolution of the vegetation. Throughout his 8-week admission, he remained well, with WCC $4.1\text{--}7.3 \times 10^9$ g/L and CRP <5 mg/L. Following 6 weeks of intravenous antibiotics, he was discharged on a 6-month course of oral Amoxicillin 3 g daily to complete treatment. Cardiac monitoring showed only Mobitz Type I heart block. Given the concurrent IE, pacemaker implant was deferred and an implantable loop recorder inserted. Endocarditis Clinic follow-up has been per protocol at 1, 3, 6, and 12 months, with TOE given the previously absent inflammatory response. This has been unremarkable for recurrent infection and embolic phenomena as of April 2021.

Discussion

IE is a known but uncommon cause of cardioembolic stroke, accounting for less than 1.5% of presentations in a 2010 Spanish

Registry.¹ The risk climbs with delays in diagnosis and falls within 48 h of appropriate antibiotics.^{7–9} This illustrates the importance of cardiac imaging when brain imaging is suggestive of a cardioembolic source. Inflammatory markers are frequently used to diagnose and prognosticate in IE, with a persistently high CRP after 1 week of antibiotic treatment an indicator of poor clinical outcome.¹⁰ This case highlights how normal inflammatory markers can be misleading and do not exclude IE.

Accounting for 0.3% cases overall and 8% of PVE, *C. acnes* IE presents unique challenges to diagnosis and management.^{11,12} It is a fastidious organism with low virulence, often requiring prolonged incubation of blood cultures, up to 14 days.^{4,12} Sterile cultures are typically discarded at 5 days incubation and even if *C. acnes* is isolated, it is often disregarded as a skin contaminant.⁵ Given that positive cultures are key to the mDC, both these factors highlight the challenges, and ultimately delays, in diagnosis.¹³ Molecular testing techniques, such as 16S rDNA PCR, are useful in direct evaluation of valve tissue when interpreted in clinical context. However, this has to be interpreted with care, as the technique involves PCR amplification of rDNA fragments, rather than culture of live organisms, and has a low sensitivity (13.6% in the largest series) in whole blood.^{2,6} However, given the benefit of identifying a causative organism in blood culture negative IE to guide appropriate treatment, the field of metagenomics may provide the sensitivity and specificity required for clinical utility.

Imaging modalities such as PET offer a particular benefit when suspicion of IE is high, despite sterile blood cultures and equivocal TOE.² PET can identify both extracardiac manifestations of IE and characteristic avidity of the valve, particularly in PVE, with sensitivity and specificity of 85–90%.^{2,14} The use of PET for diagnosis in IE has increased since the 2015 European Society of Cardiology Guidelines, for those in whom the clinical suspicion of IE remains high despite equivocal imaging/microbiology findings.¹⁵ In the absence of large prospective trials, we would continue to be cautious when PET is a diagnostic outlier compared to established components of the mDC. In our own practice, when PET is suggestive of IE we typically persist with medical management but would not consider it a lone indication for surgery.

Low virulence and ability of *C. acnes* to form biofilms may explain the lack of an inflammatory response.¹⁶ This latter ability may also explain the high rates of surgical intervention in *C. acnes* PVE despite high penicillin sensitivity, though outcomes are generally favourable following source control.^{11,12} We used Rifampicin in conjunction with a penicillin here, due to its excellent oral bioavailability, tissue penetration, and promising activity against *C. acnes* biofilms.¹⁷ This was particularly important in this case, given recurrent IE with this rare organism, suggesting treatment failure despite 6 weeks of appropriate antibiotics.

Cutibacterium acnes IE is rare but should be included in the differential of those with embolic phenomena, irrespective of normal inflammatory markers and absent fever. A prolonged course of antibiotics may be required, and surgical intervention considered where indications are present. Follow-up is often complex due to the lack of inflammatory response. This requires significant resource and a dedicated Endocarditis Team, such as the service we have established with daily joint cardiology/cardiac surgery IE input, a weekly team meeting, and dedicated outpatient clinical service.² As highlighted in this report, developing this

multidisciplinary approach is crucial to ensure excellence for clinical care, patient outcomes, and crucially, patient experience.

Patient perspective

He continues to find the uncertainty surrounding the diagnosis and appropriate management of his condition very challenging, despite the best efforts of the medical staff. In other cardiac conditions, such as congenital heart disease, there is a recognized and established service to deal with the psychological sequelae. This type of support is not typically available in IE. Devoting further resource to address the psychological burden in this chronic illness is key, as it also affects young people, results in prolonged hospital admissions and has long-term consequences.

Lead author biography



Dr Primus is a specialist registrar in cardiology at Barts Heart Centre with a sub-specialty interest in heart failure, infective endocarditis and cardiac imaging. Dr Fry is now an anaesthetics trainee in London.

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

Conflict of interest: None declared.

Funding: None declared.

Acknowledgements

The Infective Endocarditis Multidisciplinary Team, Barts Heart Centre.

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