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CASE SERIES
Congenital heart disease

Blood culture negative infective endocarditis in adult congenital heart disease patients with prosthetic grafts: a case series

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Background Blood culture negative infective endocarditis (BCNIE) is often a diagnostic challenge in adult congenital heart disease patients leading to misdiagnosis, treatment delay and associated high mortality. Studies of BCNIE in adult congenital heart disease patients repaired with prosthetic cardiovascular grafts are limited.

Case summary We report two cases of BCNIE where serology testing, multiple polymerase chain reaction testing of explanted valve material and multi-modality imaging including ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) were utilized not only to confirm the diagnosis but also to guide management strategy and inform prognosis. Both patients were treated successfully with cardiac surgery and prolonged anti-microbial therapy.

Discussion Clinical presentation of BCNIE in repaired CHD patients is highly variable. The symptoms are often non-specific with subacute or chronic presentation. This may mislead initial diagnosis and subsequent management. Multi-modality imaging including PET/CT should be considered to support the diagnosis, define the extent of infection, decide the management strategy and inform prognosis in patients. A thorough history of animal exposure, and consideration of serology and multiple molecular testing to identify the causative organism, is critical in the management of BCNIE.

Keywords Case series • Adult congenital heart disease • Blood culture negative infective endocarditis • Polymerase chain reaction • Positron emission tomography • Computed tomography

Learning points

- Clinical presentation of blood culture negative infective endocarditis (BCNIE) in repaired congenital heart disease patients is highly variable. Subacute or chronic presentation with non-specific symptoms may mislead initial diagnosis and subsequent management.
- A thorough history of animal exposure and consideration of serology and multiple molecular techniques to identify the causative organism is critical in the management of BCNIE.
- Multi-modality imaging including positron emission tomography/computed tomography should be considered to support the diagnosis, define the extent of infection, decide the management strategy and inform prognosis in patients.

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Introduction

With the growing number of patients with repaired or palliated congenital heart disease (CHD) surviving into adulthood, a variety of serious complications such as infective endocarditis (IE) are becoming increasingly frequent despite advances in medical and surgical treatment. The reported proportion of CHD in patients with IE varies between 2% and 18%[1–3] and blood culture negative infective endocarditis (BCNIE) accounts for approximately 10% of cases.[4–7] The clinical presentation of BCNIE in CHD can be highly variable, insidious, and non-specific resulting in underdiagnosis or misdiagnosis with considerable morbidity and mortality. A high index of suspicion and prompt diagnostic work up to confirm the diagnosis and identify the causative pathogen is crucial to guide appropriate treatment and improve outcome.

Standard clinical practice in the diagnosis of IE utilizes the Modified Duke Criteria which combines the findings of three domains: clinical, microbiological, and imaging. This then stratifies patients into three categories: definite, possible, and rejected IE. Blood cultures, transthoracic echocardiogram (TTE), and transoesophageal echocardiogram (TOE) are used to categorize patients by Modified Duke Criteria. Sensitivity of conventional imaging techniques such as TTE and TOE for diagnosing endocarditis in CHD is limited to 60–80%.[8] Therefore, diagnosis of BCNIE caused by intracellular organisms often requires other microbiology tests such as serology and polymerase chain reaction (PCR) as well as multi-modality imaging including computed tomography (CT) and ^{18}F-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT) particularly in cases with prosthetic cardiovascular grafts.[9] We report two cases of repaired CHD where a multidisciplinary and multi-modality approach was essential in the diagnosis and management of BCNIE.

Case presentation

Patient 1

A 48-year-old Caucasian female with a history of Tetralogy of Fallot, initially palliated with a Waterston shunt, underwent full repair with a pulmonary homograft at the age of 8 years. In 2010, she required a pulmonary valve replacement (PVR) with a 24 mm CE Perimount Magna Ease valve mounted in a Dacron graft. The patient was placed under close surveillance for progressive right ventricular outflow tract (RVOT) obstruction secondary to valve degeneration. In mid-2019, she presented with worsening constitutional symptoms such as fevers, night sweats, lethargy, and loss of appetite while being treated for lower limb cellulitis with a second course of oral antibiotics in primary care. Relevant medical history included recurrent skin infections secondary to frequent skin tears from cat scratches.

Initial work up revealed significantly elevated acute inflammatory markers and severe bicytopenia [haemoglobin 77 g/L (normal range: 115–165 g/L), white blood cell 1.7 × 109/L (normal range: 4–11 × 109/L), Neutrophil 0.4 × 109/L (normal range: 2.0–7.5 × 109/L)] which required treatment with intermittent G-CSF injections. Multiple sets of blood cultures with extended incubation were negative and the sub-optimal TTE demonstrated thickened PVR with restricted opening (*Video 1*) and elevated gradients due to PVR degeneration but it was not contributory to the diagnosis of suspected IE. Clinical suspicion for IE remained high because there was persistent elevation of inflammatory markers despite treatment with gram-positive broad spectrum antibiotics such as daptomycin which provided coverage for cellulitis. A CT scan of the chest and abdomen was chosen as the next imaging modality to (i) exclude malignancy as a cause of bicytopenia, and (ii) investigate other possible infective sources. A linear echo-density was found in the region of RVOT which we further investigated with ^{18}F-FDG PET/CT after discussion

Timeline

	Patient 1	Patient 2
Childhood diagnosis	Tetralogy of Fallot	Bicuspid aortic valve and coarctation of aorta
Surgical interventions (before teen)	Waterston shunt and then a full repair with a pulmonary homograft	Coarctation of aorta repair and Bentall procedure with a 23 mm monoleaflet Medtronic aortic valve
Further interventions	Pulmonary valve replacement with a 24 mm CE Perimount Magna Ease valve mounted in a Dacron graft	Empirically treated with 6 weeks of antibiotics for blood culture negative infective endocarditis overseas over a year before presentation
At presentation	Worsening constitutional symptoms such as fevers, night sweats, lethargy, and loss of appetite while being treated for lower limb cellulitis with a second course of oral antibiotics in primary care	Constitutional symptoms consistent of infective endocarditis such as fevers, night sweats, and lethargy
Investigation	Elevated inflammatory markers, bicytopenia, transthoracic echocardiogram (TTE) was non-contributory to the diagnosis. Computed tomography (CT) chest showed linear echo-density in right ventricular outflow tract (RVOT). ^{18}F-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT) confirmed high metabolic uptake in RVOT	TTE and transoesophageal echocardiogram demonstrated features of acute endocarditis with acute worsening of aortic valve haemodynamic and vegetation. CT and ^{18}F-FDG PET/CT showed infection extending to ascending aorta, aortic arch, and sternum

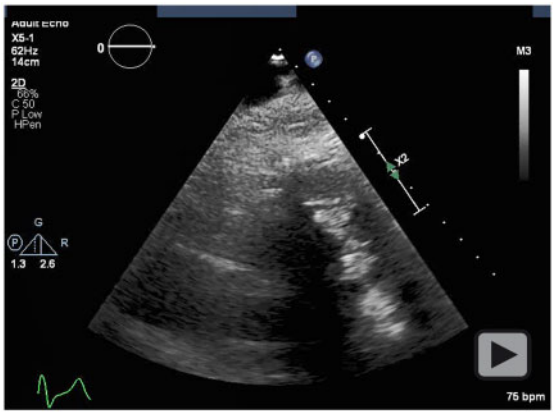
Continued

Continued

	Patient 1	Patient 2
Management	Surgical pulmonary valve and conduit replacement and prolonged antibiotics	Surgical reconstruction of the aortic root with composite graft, reconstruction of ascending aorta, aortic arch, and proximal descending aorta along with coronary re-implantation Prolonged anti-microbial therapy
Follow-up	Complete normalization of bicytopenia and inflammatory markers Remained well with satisfactory pulmonary valve haemodynamic at 12 months after surgery	Four-fold reduction in his acute phase (Phase 2) IgG titre with negative real-time polymerase chain reaction at 5 months post-cardiac surgery Clinically well with satisfactory echocardiographic findings

in the adult congenital multidisciplinary team (MDT) meeting. This confirmed the presence of high metabolic uptake in the RVOT (*Figure 1*) and ruled out other infective sources and malignancy.

Consequently, the patient underwent surgical pulmonary valve and conduit replacement as she was failing anti-microbial therapy. Intraoperatively, the conduit was found to be severely narrowed in the proximal anastomosis with vegetations in the pulmonary valve. Real-time PCR from the explanted valve was positive for *Staphylococcus aureus* and 16s broad range PCR was positive for *Bartonella henselae* ultimately confirming the diagnosis of cat-scratch disease and IE. Post-operatively, she was treated with 6 weeks intravenous ceftriaxone and gentamicin followed by further 6 weeks of oral doxycycline resulting in complete resolution of constitutional symptoms, inflammatory markers, and normalization of bicytopenia. The patient remained well with satisfactory pulmonary valve haemodynamics at 12 months following surgery.



Video 1 Transthoracic echocardiogram (parasternal short-axis view) of Patient 1 demonstrating thickened pulmonary valve replacement with restricted opening.

Patient 2

A 32-year-old Caucasian male from Sardinia with a history of bicuspid aortic valve and repaired coarctation of aorta had a Bentall procedure with a 23 mm monoleaflet Medtronic aortic valve for aortic regurgitation with associated aortopathy of proximal ascending aorta. This surgery was carried out in an overseas centre in Southern Europe at the age of 12 years. In 2017, the patient first presented to our centre with clinical symptoms suggestive of IE on a background of BCNIE overseas over a year ago. Importantly, he was empirically treated with 6 weeks of antibiotics without identification of a causative organism at the time.

With the acute presentation, multiple sets of blood cultures remained negative despite acute worsening of aortic valve haemodynamics and presence of vegetations in the mechanical aortic valve and aortic graft on TTE and TOE (*Videos 2* and *3*). Preoperative planning CT chest suggested potential infective involvement of ascending aorta and aortic arch. After discussion in the MDT, ^{18}F-FDG PET/CT was carried out to define the extent of infection and guide the surgical management. This demonstrated an extensive metabolic uptake involving the mechanical aortic valve, ascending aorta, aortic arch, and the sternum (*Figure 2A and B*). Subsequently, the patient was found to have a positive PCR for *Coxiella burnetii* in serum along with high level titre for Phase 2 (acute phase) IgG and low level titre for Phase 2 IgM which is highly suggestive of chronic aortic graft and mechanical aortic valve endocarditis due to Q fever.

The patient underwent cardiac surgery involving reconstruction of the aortic root and ascending aorta with 25 mm biointegral composite graft, bovine pericardial patch reconstruction of aortic arch and proximal descending aorta along with coronary re-implantation. The explanted mechanical valves and tissues had positive realtime PCR for *C. burnetii* though 16s broad range PCR was negative. Following surgery, the patient received prolonged treatment with oral doxycycline and hydroxychloroquine by the microbiology team.

Repeat convalescence Q fever antibodies titres (*Table 1*) showed a significant four-fold reduction in his acute phase (Phase 2) IgG titre with negative real-time PCR at 5 months post-cardiac surgery. The patient continued to receive oral doxycycline and hydroxychloroquine therapy with serial monitoring of *Coxiella* Serology (*Table 1*).

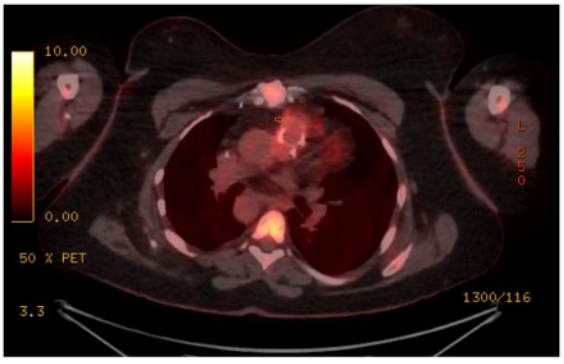
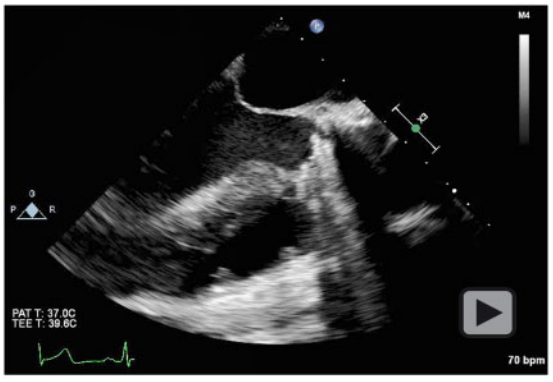
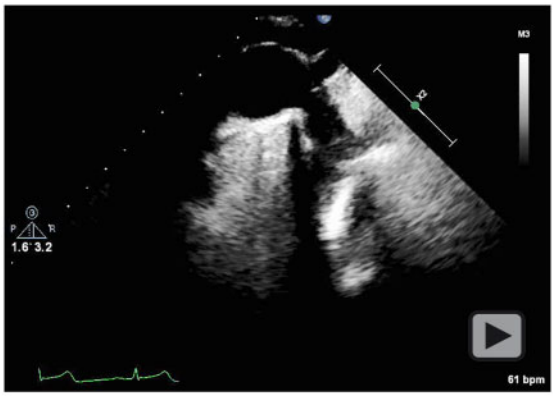


Figure 1 ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography axial view of Patient 1 demonstrating increased activity in right ventricular outflow tract below the bioprosthetic pulmonary valve replacement.



Video 3 Transoesophageal echocardiogram (mid-oesophageal view at 120°) of Patient 2 showing mobile vegetation in the left ventricular outflow tract side of mechanical aortic valve and thick aortic root with an area of echo free space consistent with aortic root abscess.



Video 2 Transthoracic echocardiogram (suprasternal view) of Patient 2 demonstrating mobile vegetation at the site of previous aortic arch graft.

Discussion

True BCNIE caused by intracellular organisms such as *Coxiella* and *Bartonella* is increasingly reported in patients with underlying heart disease across Europe.[10–12] The clinical manifestation can be protean and non-specific resulting in considerable diagnostic and therapeutic dilemma and mortality.

Our first case demonstrated acute on sub-acute presentation of right-sided endocarditis due to two pathogens namely, *B. henselae* and *S. aureus* in a patient with surgically repaired Tetralogy of Fallot and significant residual haemodynamic lesion in the homograft PVR. The symptoms were non-specific, and there was severe bicytopenia due to bone marrow suppression as a result of chronic *Bartonella* infection. Blood cultures were negative because (i) *Bartonella* is an intracellular pathogen that does not grow well in routine blood cultures and (ii) *S. aureus* was partially treated with antibiotics in primary care. Diagnosis of BCNIE was confirmed in this case by ^{18}F-FDG PET/CT and PCR of the explanted conduit. Serology for *Bartonella* was not carried out initially after consultation with microbiology as there was sufficient evidence from other diagnostic modalities and a significant chance of sero-reactivity caused by previous infection secondary to cat scratches. ^{18}F-FDG PET/CT was chosen over TOE in this case due to expected poor views with the anterior position of the pulmonary valve and RVOT.

The second case exemplified an acute presentation of left sided endocarditis due to *C. burnetii* in a patient with prosthetic aortic material. The patient likely had previous animal exposure during his childhood in the rural area in Sardinia which is a farming and agricultural community. We believed his previous partially treated BCNIE was caused by the same pathogen. Though he fulfilled the Modified Duke criteria to diagnose endocarditis, serology and multiple molecular techniques were required to determine the causative organism. While ^{18}F-FDG PET/CT defined the extent of the infection, it also provided crucial information to guide surgical management and inform perioperative risk and prognosis to the patient.

The Modified Duke Criteria provides a reference framework for diagnosing IE but it performs poorly in patients with CHD repaired or palliated with prosthetic material. It also performs poorly if the endocarditis is caused by a fastidious intracellular organism. Application of non-conventional microbiology testing with serology and molecular techniques along with multi-modality imaging is critical in such patients if the clinical suspicion remains high despite negative blood cultures, in order to aid the diagnosis and select an appropriate treatment. Out of all serology for fastidious organisms, *Coxiella* and *Bartonella* serology have been found to be highly contributory in the diagnosis of BCNIE.[13] As such, the latest European Society of Cardiology guideline recommends routine use of *Coxiella* and *Bartonella* serological testing in patients with BCNIE, and ^{18}F-FDG PET/CT in the assessment of prosthetic valve infection when echocardiogram is inconclusive.[9]

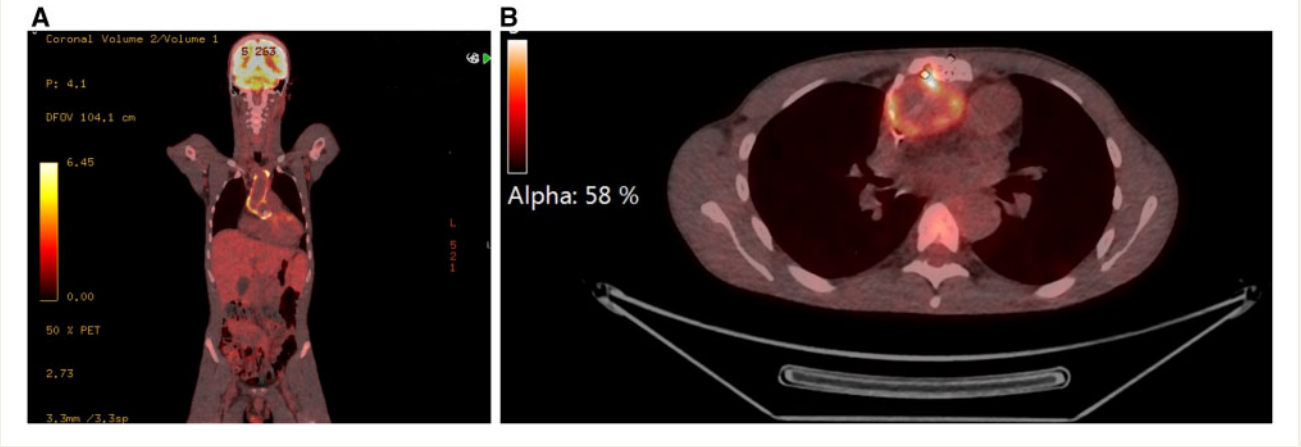


Figure 2 ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography. (*A*) Coronal view and (*B*) axial view of Patient 2 demonstrating marked increase in activity involving the aortic root, ascending aorta, and proximal aortic arch consistent with severe infection/inflammation secondary to blood culture negative infective endocarditis.

Table 1 **Serial Coxiella Serology**

Date	30 September 2017	17 October 2017	27 February 2018	19 December 2018	02 December 2019
Month	0	0.5	5	15	27
Phase 1 IgG	10240	5120	5120	5120	2560
Phase 1 IgA	1280	5120	640	320	160
Phase 2 IgG	40960	10240	10240	10240	10240
Phase2 IgM	640	2560	0	0	0
PCR	Positive	Negative	Negative	Negative	Negative

However, it is important for clinicians to recognize the limitation of these tests, and thereby utilize them as a complementary investigation tool in aiding diagnosis rather than a standalone diagnostic tool. Limitations of serology tests include sero-cross-reactivity from another organism or sero-reactivity from prior exposure. For PCR assays, testing histology specimens with organism-specific PCR assays is more sensitive than blood, due to a relatively higher abundance of bacterial DNA in histology specimens.[14,15] It has been shown that the broad range 16S rDNA PCR assay was able to provide additional diagnostic value in 62% of BCNIE cases.[16] Studies comparing TTE and TOE with ^{18}F-FDG PET/CT in evaluating patients with suspicious IE found that ^{18}F-FDG PET/CT can provide a significantly superior diagnostic yield.[17–19] However, it is worth noting that ^{18}F-FDG-PET/CT uptake is often identified in recently implanted prosthetic valves, where uptake can remain increased at 1 year after surgery.[20] Additionally, ^{18}F-FDG as a metabolic substrate is frequently up taken by the left ventricle in the absence of infection, and this can make assessment more difficult, although methods of suppression of myocardial uptake can be used.[21]

Once the organism is identified in BCNIE, prolonged anti-microbial treatment is often necessary to eradicate the infection and prevent recurrence. The recommended treatment for *Bartonella* endocarditis is a beta-lactam antibiotic or doxycycline for four weeks in combination with gentamicin for the first 2 weeks. For *Coxiella* endocarditis, the treatment is doxycycline and hydroxychloroquine until Phase 1 antibody titre is <800 for IgG and <50 for IgM.[9,22] However, antimicrobial treatment alone is often insufficient because prostheses are usually polytetrafluoroethylene tubes, which requires surgical re-intervention to explant the contaminated foreign material.

In summary, with more CHD patients surviving into adulthood as a result of improved paediatric care and surgical techniques, serious long-term complications including IE are increasingly common. It is very important that clinicians recognize the atypical presentation of BCNIE, the diagnostic pathway, and utilize a multi-modality approach of imaging, serology testing and PCR of explanted valve material to confirm the diagnosis and identify the causative organism. In particular, we believe that ^{18}F-FDG PET/CT should be routinely considered in high-risk cases with prosthetic cardiovascular grafts to support the diagnosis, quantify the extent of the infection, define management strategy and inform prognosis.

Lead author biography

Dr Myo Thidar Lwin completed her undergraduate education at the University of Medicine 2, Yangon, Myanmar. She then completed her general physician and cardiology training in Queensland, Australia and Adult Congenital Heart Disease fellowship at University Hospital Southampton NHS Foundation Trust before taking on her current role as a locum adult congenital cardiologist. Her clinical and research interests in adult congenital heart disease include imaging, pregnancy, and pulmonary hypertension. She aims to pursue a formal research degree in adult congenital heart disease.

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.

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