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CASE REPORT
Valvular heart disease

Blood culture-negative *Haemophilus* endocarditis with large vegetation and the role of bronchoalveolar lavage: a case report

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Background Blood culture-negative endocarditis (BCNE) is a significant condition associated with cardiac vegetation. It often occurs alongside sepsis, auto-immune diseases, or malignancies, posing a risk of vegetation and embolization. Notable pathogens include *Haemophilus* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species.

Case summary A 60-year-old white male Belgian patient presented with worsening dyspnoea. His recent medical history included chronic infections over the past 6 months. Transthoracic echocardiography revealed severe aortic stenosis with an 18 × 12 mm vegetation. Despite normal inflammatory markers and negative blood tests, 18F-fluorodeoxyglucose positron emission tomography with computed tomography excluded malignancy but identified multiple bilateral septic lung emboli. Sputum cultures and tuberculosis polymerase chain reaction (PCR) were negative. Facing the high risk of cardiac embolization and the need for aortic valve replacement, surgery was scheduled with an intraoperative bronchoalveolar lavage (BAL) to investigate the lung lesions. Intraoperative findings confirmed valvular lesions, and a biological aortic valve was successfully implanted. The post-operative course was uneventful. Aortic valve cultures and eubacterial PCR results were negative, but BAL cultures were positive for *Haemophilus influenzae*, indicating a chronic infection. The patient showed favourable progress at 6 months post-surgery with ongoing antibiotherapy.

Discussion This case illustrates a rare BCNE associated with large vegetation and symptomatic *H. influenzae* chronic respiratory tract colonization (CRTC). For BCNE cases with negative sputum cultures and suspected bacterial CRTC, we recommend performing BAL cultures for accurate diagnosis.

Keywords Negative blood culture • Endocarditis • Large vegetation • *Haemophilus* • Bronchoalveolar lavage • PET/CT • Case report

ESC curriculum 2.2 Echocardiography • 2.5 Nuclear techniques • 4.11 Endocarditis • 4.2 Aortic stenosis • 7.5 Cardiac surgery

Learning points

- To be able to investigate a negative culture endocarditis with a vegetation.
- To know the aim of bronchoalveolar lavage in the management of patients with negative culture endocarditis and pulmonary lesions.
- To know the association between large size vegetation and bacterial endocarditis, especially the HACEK group.

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Introduction

Endocarditis can be caused by bacterial, fungal, or mycobacterial infection.[1] The aetiology of endocarditis may also be non-infectious, due to auto-immune disease (Libman–Sacks, paraneoplastic syndrome)[2] or eosinophilic disease (Loeffler endocarditis).[3] Excluding a previous infectious aetiology is challenging among patients without any clinical presentation of an infective endocarditis (IE; e.g. fever, high C-reactive protein, positive procalcitonin, leucocytosis, and positive haemoculture) and with confirmed valve vegetation on echocardiography. Furthermore, data and recommendations from medical societies in establishing the diagnosis are limited.

Summary figure

This clinical case describes a dyspnoeic patient who was previously treated for a bacterial sinusitis 5 months before his admission and was found to have a large aortic valve vegetation without any fever or inflammatory syndrome. We report the discussion regarding the diagnostic and therapeutic management of a *H. influenzae* infection, which was diagnosed by BAL cultures.

Case presentation

A 60-year-old white Belgian male was referred due to progressively worsening dyspnoea classified as NYHA class III over several

Timeline of critical events in the assessment of dyspnoea and blood culture-negative endocarditis

Initial assessment of the dyspnoea	
Initial relevant clinical evaluation	Admission for a progressing dyspnoea New York Heart Association (NYHA) class III over several months. Active tobacco use. Previous use of antibiotherapy for bacterial sinusitis 5 months ago. Normal vital parameters. No fever. Clinical exam: aortic systolic murmur.
Initial blood analysis	No inflammatory syndrome, normal blood count cells, N-terminal pro b-type natriuretic peptide (NT-proBNP) 709 ng/L (normal < 400 ng/L), normal thyroid tests.
Transthoracic echocardiography (TTE)	Hyperkinetic left ventricle. Severe aortic stenosis (medium gradient: 51 mmHg; aortic valve area: 0.8 cm^2; maximal transaortic velocity: 4.87 m/s). Moderate aortic regurgitation (Grade 2/4). Large aortic valve vegetation.
Primary investigational assessment of the negative blood culture endocarditis without inflammatory syndrome	
Blood analysis	Bacteriology: normal blood cultures. Serology: normal for *Coxiella burnetii*, *Francisella tularensis*, and Bartonella species, *Tropheryma whipplei*, hepatitis, human immunodeficiency virus, and syphilis.
Sputum analysis	Normal mycobacterial polymerase chain reactions (PCRs) and cultures. Normal bacterial cultures.
Transoesophageal echocardiography (TEE)	Confirmation of a 18 × 12 mm aortic valve vegetation.
Thoraco-abdominal computed tomography	Ground-glass opacifications in both lungs, associated with septic emboli. Mediastinohilar lymph nodes of sub- and peri-centimetric size.
Secondary investigational assessment of the lung lesions	
Total body positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography	No active neoplasia. Ground-glass opacification in both lungs, characterized by modest tracer accumulation.
Immunology analysis	Normal level of antibodies: IgM, IgG, IgA, C3, C4, rheumatoid factor, antinuclear, anti-neutrophil cytoplasmic, anticardiolipin, lupic anticoagulant, and anti-β2-glycoprotein.
Heart team decision: pre-operative bronchoscopy with bronchoalveolar aspiration and lavage, followed by surgical biological valve replacement. Pre-operative treatment with doxycycline.	
Aortic valve biopsy analysis	Bacteriology: normal cultures and eubacterial PCRs. Pathology: no signs of Libman–Sacks endocarditis, no bacterial infection, no fungal infection, and no malignancy.
Empiric post-operative antibiotherapy	Post-operative empirical antibiotherapy during 6 days by meropenem, vancomycin, and doxycycline.
Bronchoalveolar lavage (BAL) analysis on day 6 after surgery	Bacteriology: positive aspiration (+) and lavage (++) cultures after 6 days of incubation (*Haemophilus influenzae*). Negative mycobacterial cultures and PCRs. Cytopathology: bronchial cells, alveolar macrophages, and squamous cells. Few slightly irregular groups of cells without malignancy.
Discharge and definitive antibiotherapy	Four days of oral antibiotherapy by cefuroxime and ciprofloxacin according to the antibiogram of *H. influenzae*. Discharge of the patient 48 h after initiating oral antibiotherapy.

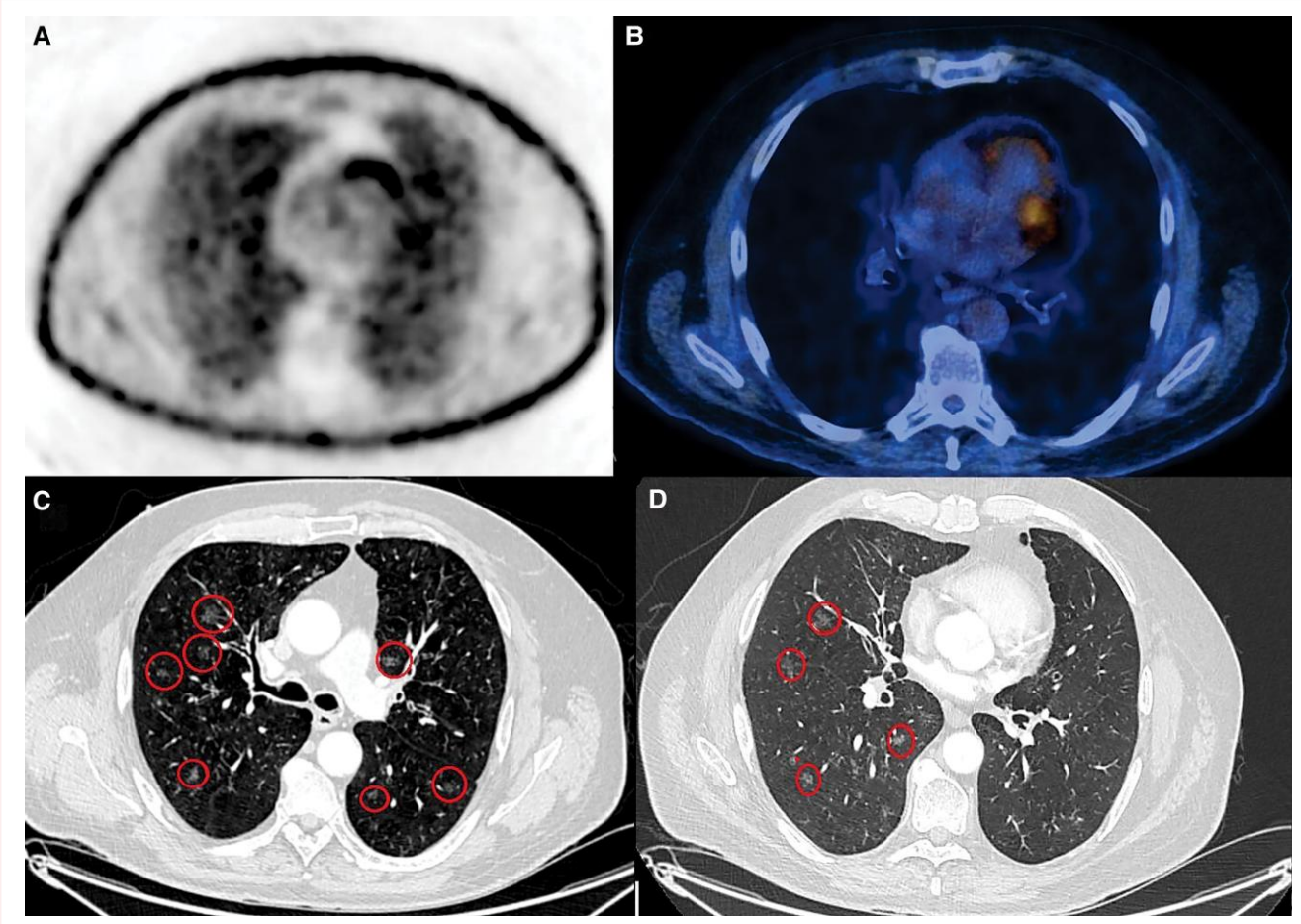

Figure 1 Axial thoracic views from positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (*A* and *B*) and angio-computed tomography scan (*C* and *D*) reveal a random distribution of diffuse ground-glass opacities in both lung fields (marked with red circles), accompanied by moderate 2-deoxy-2-[fluorine-18]fluoro-D-glucose uptake, indicative of multiple septic emboli.

months. Five months prior his presentation, the patient has been treated for sinusitis with clindamycin for 10 days. The patient had a history of chronic obstructive pulmonary disease (COPD), transient ischaemic attack, active tobacco use, class I obesity, hypercholesterolaemia, and peripheral vascular disease. He experienced an anaphylactic shock following the administration of a ceftriaxone in the past. The clinical exam demonstrated a holosystolic aortic murmur without any other signs of infection. There are no signs of petechiae, splinter haemorrhages, Osler nodes, Janeway lesions, or Roth spots.

Transthoracic echocardiography and TEE showed severe aortic stenosis (medium gradient: 51 mmHg; aortic valve area: 0.8 cm^2; maximal transaortic velocity: 4.87 m/s) with moderate aortic regurgitation and a hyperkinetic left ventricle. Transoesophageal echocardiography confirmed the 18 × 12 mm aortic valve vegetation.

Thoraco-abdominal angio-computed tomography (angio-CT) showed ground-glass opacification in both lungs, raising suspicion of septic emboli (*Figure 1*). Total body positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (^{18}F-FDG-PET/CT) ruled out an active neoplasia and confirmed ground-glass, characterized by modest tracer accumulation (*Figure 1*). The laboratory investigations revealed normal blood cell count, C-reactive protein, procalcitonin, blood cultures (details are provided in the Supplementary material), and infectious serologies (*C. burnetii*, *F. tularensis*, and *Bartonella* species, *T. whipplei*, human immunodeficiency virus and syphilis, and viral hepatitis B and C). Three sputum tuberculosis analyses with cultures and PCR showed no active tuberculosis. N-terminal pro b-type natriuretic peptide was 709 ng/L, and high-sensitivity cardiac troponin T (hs-cTnT) was 12 ng/L.

The patient underwent surgical biological valve replacement upon recommendation of the heart team, which includes cardiologists, heart surgeons, infectiologists, and anaesthesiologists.

Despite a lack of positive cultures and no inflammatory syndrome, the infectious disease specialist proposed initiating pre-operative antibiotic therapy with ceftriaxone and doxycycline before the planned aortic valve replacement due to the potential risk of bacteraemia from the pulmonary septic emboli. However, the patient experienced an anaphylactic reaction to ceftriaxone in the past and had no episodes of bacteraemia since completing a course of clindamycin 5 months ago. Given the potential risks associated with beta-lactam antibiotics, our team decided to proceed with doxycycline monotherapy to cover slow-growing pathogens, like *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* (HACEK group), or *Brucella* species, while awaiting laboratory test results.

Pre-operative coronary angiography was normal. Bronchoalveolar lavage was done before surgery to investigate the pulmonary septic

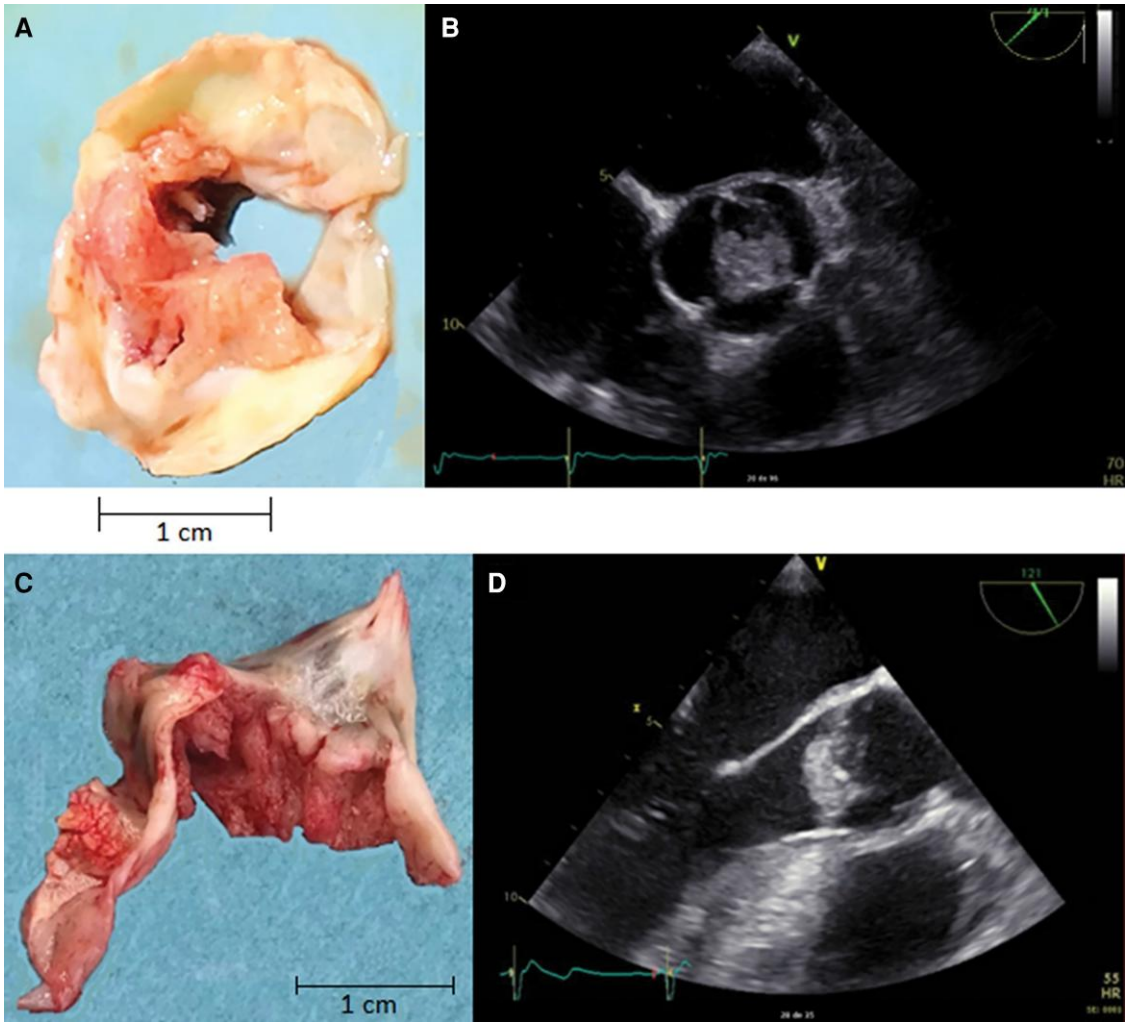

Figure 2 Anatomical infra-valvular (*A*) and supra-valvular (*C*) views are depicted. Transoesophageal echocardiographic views show the aortic valve and its vegetation in both short-axis (*B*) and long-axis (*D*) orientations.

emboli. The aortic valve was completely removed (*Figure 2*) and replaced with a biological aortic valve implant.

The aortic valve biopsy histocytopathology, broad-range PCRs, and cultures were negative. Bronchoalveolar lavage cultures showed pan-sensitive *H. influenzae*.

The patient's chronic pulmonary infection was treated with meropenem, vancomycin, and doxycycline, followed by cefuroxime and ciprofloxacin according to the antibiogram of *H. influenzae* for 10 days. The patient was discharged on the eighth day following his surgery. Follow-up after several months shows an improvement in dyspnoea to NYHA stage II and a resolution of the septic emboli on thoracic CT scan following antibiotic treatment. The persistence of dyspnoea is attributed to the underlying COPD, classified as stage II, group D according to the current Global Initiative for Chronic Obstructive Lung Disease classification in 2022.

Discussion

Bacterial endocarditis is associated with fever, systemic embolisms, heart failure, and valve dysfunction. The HACEK group are Gram-negative bacteria and a rare cause of IE. The pathogenesis of HACEK endocarditis is frequently caused by bacterial translocation following trauma, procedures, or local infection.[4,5] These pathogens grow slowly in cultures[6] and may even result in negative cultures.[7] The growth of HACEK in culture can be enhanced by adding carbon dioxide in the medium culture.[7] Large vegetations above 10 mm have been reported with HACEK endocarditis.[8–10] *Haemophilus* infections have been associated with prior dental work or upper respiratory tract infection[11] and cause less than one percent of all IE.[12] Time to diagnosis varies between 2 days and 1 year because of the subacute onset of *Haemophilus* endocarditis.[13]

In a study by Dayer *et al.*,[14] 8.3% of IE cases were classified as blood culture-negative endocarditis (BCNE). History taking of symptoms, risk factors, infection and antibiotic use history, patient's environment, presence of animals, and travel history need to be rigorously investigated in order to find the aetiology of infection.

Laboratory investigations should be used to differentiate bacterial from non-bacterial aetiologies. Three sets of blood cultures, each including one aerobic and one anaerobic bottle, should be drawn from different venipuncture sites, with at least one hour between the first and last samples.[15] Tuberculosis and fungal infections should be ruled out in cases of immunodeficiency, such as human immunodeficiency virus or viral hepatitis infections. Broad-range PCR amplification in

blood or native valve should be used only if all pre-operative investigations are negative.[16] Bronchoalveolar lavage culture could be done if any pulmonary infection aetiology is still suspected.

Large vegetation may be caused by the ability of bacteria to attach and grow on the endocardium. Vegetation's characteristics depend on rheological factors and prior valve injuries. Vegetations in non-infectious endocarditis are usually small (<1 cm), and large vegetations suggest a bacterial aetiology.[17] Transthoracic echocardiography and TEE should be done to examine any vegetations.

The ^{18}F-FDG-PET/CT can be used to identify intracardiac lesions, bacterial disseminated disease (septic emboli), neoplastic or metastatic lesions. The ^{18}F-FDG-PET/CT has a central role and should be done as soon as possible, because the decrease of inflammation caused by antibiotic therapy can increase the rate of false negative findings, especially when C-reactive protein falls under 40 mg/L.[18]

In the 2023 European Society of Cardiology endocarditis guidelines,[19] no strategies for patients with normal laboratory tests and confirmed valve vegetation without any clinical signs of IE are defined. In the literature, the utility of BAL cultures in BCNE has not previously been described. This case report illustrates the potential utility of BAL in the care of patients with BCNE and visible lung lesions on CT, in order to facilitate the early identification of the causative pathogen and narrow the broad-spectrum antibiotic treatment.

Moreover, no studies or guidelines have specifically addressed the comparison between peri-operative empirical antibiotic prophylaxis and post-operative antibiotic prophylaxis alone to identify the causative pathogens of BCNE in patients without any symptoms.

Conclusion

To our knowledge, this is the first reported case of a patient with BCNE, in which BAL was used to diagnose a *Haemophilus* endocarditis. The low-grade endocarditis was treated concomitantly to the previous sinusitis treatment by antibiotics. Further work is required to evaluate the utility of BAL cultures for the care of patients with BCNE and concomitant pulmonary infection. Additional studies are also needed to assess the use of empirical antibiotherapy in patients with BCNE who show no signs of infection, such as fever, elevated C-reactive protein, or leucocytosis.

Lead author biography

Dr Samaksha Pant, born in Geneva in 1991, completed his medical training at the University of Geneva, where he developed a strong interest in cardiology and palliative care. Throughout his career, Dr Pant pursued diverse experiences and underwent rigorous training in various Swiss hospitals. These experiences enhanced his clinical skills and deepened his understanding of patient care, particularly in the geriatric community. Dedicated to improving the quality of life of elderly patients, Dr Pant combines clinical expertise with a strong interest in research. His work aims to bridge the gap between cardiology and palliative care to improve patient outcomes and overall well-being, particularly among patients with heart failure.

Supplementary material

Supplementary material[8–10,12,17,20,21] is available at *European Heart Journal – Case Reports* online.

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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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