Case Report

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Culture-negative endocarditis with multifocal spread and flail mitral valve leaflet: a case report

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Introduction: Blood culture-negative infective endocarditis is the condition in which a causative organism cannot be identified after inoculation of at least three samples using standard blood-culture systems for 7 days. It has a low reported incidence of about 2.5–31%. Causes may be infectious or non-infectious; use of prior antibiotic therapy is usually the leading factor.

Case presentation: The authors present a case of true culture-negative endocarditis involving the mitral valve, with multiple foci of spread including brain, spleen, liver, and Intervertebral disc, which remained persistent despite treatment with intravenous broad-spectrum antibiotics on an inpatient and outpatient basis but eventually improved after upgrading alternative broad-spectrum antibiotic for an extended duration. The patient had complications in the form of a flail mitral valve with persistent mitral regurgitation, requiring mitra-clip placement.

Discussion: Positive blood culture is one of the major diagnostic criteria to establish infective endocarditis. Patients may have persistent negative cultures due to previous antibiotic use, the presence of fastidious organisms, or the use of inappropriate techniques or media. Involvement of a multidisciplinary team, use of multimodal investigations, and appropriate antibiotic stewardship are crucial. Extended duration of treatment and upgrading antibiotics can be helpful next steps in highly suspicious cases. With multifocal spread as in our case, it further becomes challenging to control and treat the infection as it is frequently connected with higher morbidity and mortality.

Conclusion: Blood culture-negative endocarditis is an entity that can present with early complications. It is diagnostically and therapeutically challenging to treat such patients. Multimodal approaches for early diagnosis and appropriate treatment are crucial owing to its high morbidity and mortality.

Keywords: transthoracic echocardiography, flail mitral leaflet, multifocal brain abscesses, blood culture-negative endocarditis

Introduction

Blood culture-negative infective endocarditis (BCNE) is defined as endocarditis in which a causative organism cannot be identified after inoculation of at least three samples using standard blood-culture systems for 7 days[1]. The presence of a negative culture status could be owing to the prior usage of antibiotics before culture or may be due to the involvement of difficult-to-culture microorganisms[2–4]. Regardless of the cause, BCNE can be a diagnostic and therapeutic challenge to a physician. It can have varied presentations. Appropriate evaluation and choice of therapeutics depending on the patient's demographic and epidemiology is paramount[5]. Here, we present a case of a 54-year-old male with BCNE and a cluster of complications like splenic, liver, brain abscess, and mitral vegetation complicated as a flail mitral valve which later spread to the intervertebral disc. This case has been reported in line with the SCARE 2020 guidelines[6].

HIGHLIGHTS

- Blood culture-negative infective endocarditis is the condition in which a causative organism cannot be identified after inoculation of at least three samples using standard blood-culture systems for 7 days.
- Patients may have persistent negative cultures due to previous antibiotic use, the presence of fastidious organisms, or inappropriate techniques or media.
- Both diagnostic and therapeutic approaches towards blood culture-negative infective endocarditis can be a demanding task for a physician.
- Involvement of a multidisciplinary team, use of multimodal investigation, and appropriate antibiotic stewardship are crucial.
- With multifocal spread as in our case, it further becomes challenging to control and treat the infection as it is frequently connected with higher morbidity and mortality.

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Case presentation

A 54-year-old male presented to the emergency department with a 2-week history of vague abdominal discomfort associated with nausea and multiple episodes of non-projectile vomiting. Two days prior, he developed intermittent fever associated with chills. The maximum documented temperature was 38.5°C. The symptoms were associated with headache, dizziness, a gradual diminution of vision of bilateral eyes, and ringing sensation in bilateral ears. He did not have any comorbidities. There was no history of anorexia, night sweats, and significant weight loss. He worked as a chef in a Chinese restaurant and was involved in handling meat and meat products. He did not smoke or consume alcohol. At the time of presentation, he was febrile. Physical examination revealed a systolic murmur on the apical area. Extraocular movements were sluggish. Apart from this, he had poor dental hygiene with multiple carious teeth with no prior dental treatment.

Routine laboratory evaluations showed leukocytosis and elevated erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP). Computed tomography (CT) scan of the abdomen showed an abscess in the right lobe of the liver and a possible splenic abscess. MRI brain revealed a $1.1 \times 2.1 \times 1.2$ cm thick-walled cystic lesion in the left parietal lobe with T1 hypo intensity, T2/FLAIR hyperintensity, and restricted diffusion consistent with abscess draining into the left ventricular system causing ventriculitis, choroid plexus, and focal meningitis as illustrated in Figure 1. Electrocardiogram (ECG) was unremarkable. With the presence of a systolic murmur and multiple foci of abscess in the brain and abdomen, a cardioembolic aetiology was suspected. A transthoracic echocardiogram was performed which showed a 1×0.5 cm mitral valve vegetation with a flail mitral valve and moderate eccentric mitral regurgitation as shown in Figure 2. The size of cardiac chambers, global systolic function, and left ventricular ejection fraction as seen on the echocardiogram were normal.

The patient was attended by a team of neurosurgeons, cardiologists, infectious disease specialists, dental physicians, and critical care physicians in intensive care settings. Empirical broad-spectrum antimicrobial coverage was done with intravenous vancomycin, cefepime, and metronidazole. In the meantime, a blood culture and sensitivity test were done which revealed no growth of microorganisms. Repeat culture did not show growth as well. As per the attending team of the neurosurgeon, there was no need for immediate surgery, however, intravenous dexamethasone was started for vasogenic cerebral oedema. Levetiracetam was started for seizure prophylaxis.

Cerebrospinal fluid analysis was not done taking into consideration the risk of herniation ascribed to immense vasogenic cerebral oedema. Taking into consideration the likelihood of BCNE, an elaborate history concerning the presence of predisposing factors for BCNE was taken. He denied notable outdoor exposure, or contact with stray or farm animals, and did not recall a history of tick bites, pet scratches or bites, or contact with sick patients. He also denied a history of illicit drug abuse. Polymerase chain reaction (PCR) for fastidious organisms including Bartonella, Brucella, Coxiella, and Trophyrema was negative. Screening for legionella, mycoplasma, chlamydia pneumonia, anaerobic fungal culture aspergillus, candida as well as autoantibodies including anticardiolipin, and antiphospholipid was negative.

Extraction of multiple carious teeth 1, 3, 4, 9, 10, 26, and 27 was done by a dental team and the antibiotic therapy was switched to vancomycin and meropenem. His clinical conditions gradually improved, the echo showed a diminution of vegetation size, and further approach was stepped down from the intensive care unit to the hospital floor unit. Later, he was discharged on oral co-trimoxazole for the next 2 weeks. The dose of dexamethasone was tapered. Repeat MRI and echocardiogram were planned on follow-up visits.

The patient stated that he had been well-compliant with the antibiotics prescribed. But, on the follow-up visit, there was a new onset of lower back pain which started a week ago. The pain was

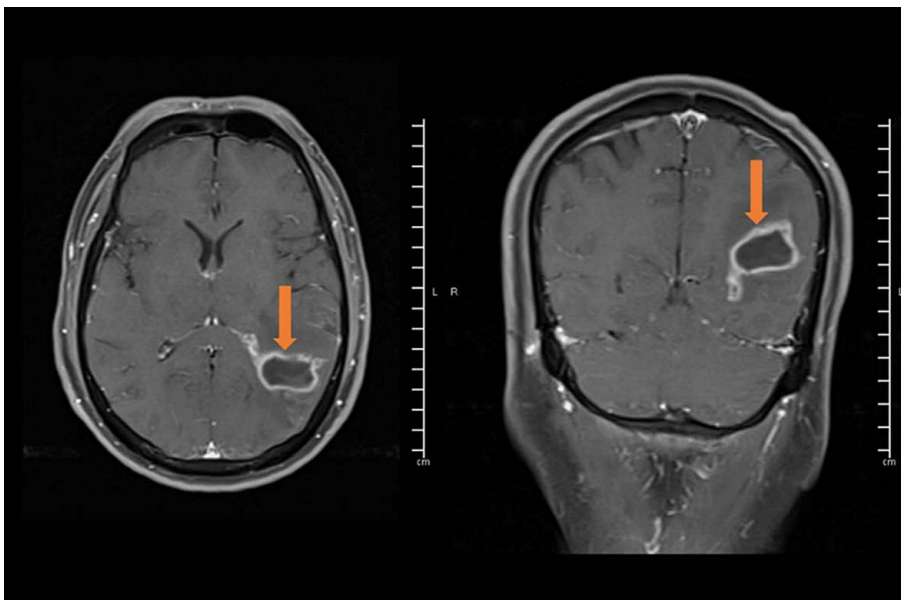

Figure 1. MRI head coronal and axial view showing left parietal abscess and surrounding oedema (marked by the arrows).

dull aching, moderately severe, persistent, and aggravated with movement and postural changes. There was no history of recent trauma or fall injury. He did not have a history of incoordination, weakness, seizure, syncope, loss of consciousness, and behavioural disturbances. On re-evaluation, he was afebrile and did not have neck stiffness. However, the left lumbar area was tender. Salient findings on MRI Lumbosacral spine were the features suggestive of osteomyelitis and discitis of L3–L4 vertebrae (Fig. 3). A disc core biopsy specimen was taken under CT guidance which showed no growth on culture. Repeat echocardiography showed persistence of mitral vegetation (1×0.5 cm), which was slightly larger in comparison to what was noted earlier with moderate eccentric mitral regurgitation. However, repeated MRIs brain showed resolution of the parietal lobe abscess. The patient was readmitted. He was attended by a neurosurgery team who denied the need for any active surgical intervention. Basal metabolic panel testing showed a slight rise in blood creatinine level (1.5 mg/dl). Three sets of blood cultures were performed during his re-admission, all of which were negative. The cardiovascular team was consulted for enlarging valvular vegetation. A transesophageal echocardiogram (TEE) was not done due to prevailing infection and also, it would not alter the current management approach. A thorough analysis and discussion between the cardiovascular team and infectious disease specialist team led to the decision to upgrade the antibiotics while having the patient under close observation and rapidly intervening in case of failure to respond. For now, he was not considered for a surgical approach. So, the patient was started on intravenous daptomycin and piperacillin-tazobactam. The pain was managed with Tylenol, topical diclofenac, and lidocaine patches.

Upon completion of the 6-week antibiotics course, the patient had clinically improved with down-trending inflammatory markers. TEE revealed the resolution of vegetation. Creatinine level had declined. There was no pain or fever. Physical examination was unremarkable except for a soft systolic murmur on the precordium. He was re-assessed in a follow-up visit 2 weeks later. The patient had persistent mitral valve prolapse as a complication and was scheduled for Mitra-clip placement.

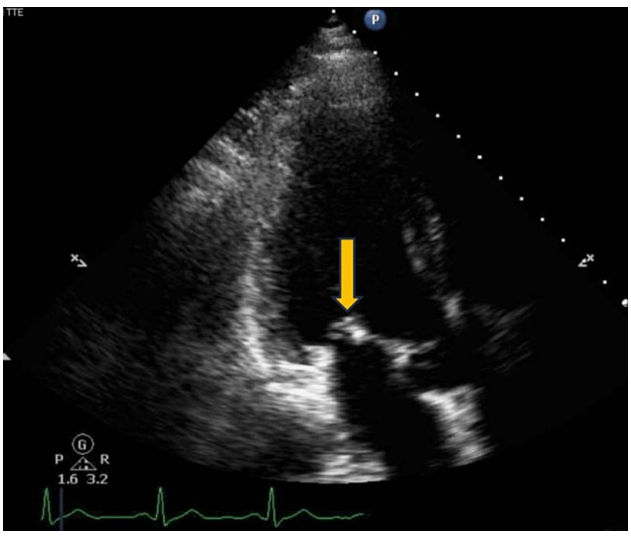

Figure 2. A transthoracic echocardiogram showing mitral valve vegetation with a flail mitral valve (marked by the arrows).

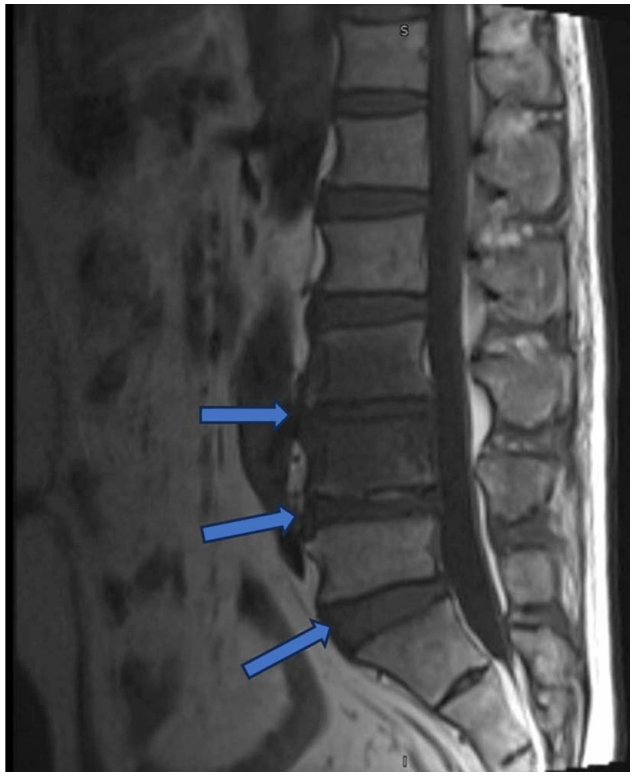

Figure 3. MRI of lumbosacral spine showing features suggestive of osteomyelitis and discitis of L3–L4, L4–L5, and L5–S1 vertebrae level (marked by the arrows).

Discussion

BCNE is a rare occurrence with a reported incidence of about 2.5–31%[7]. Both infectious and non-infectious causes lead to BCNE. Amongst all, prior antibiotic therapy stands as the leading cause of BCNE[3,8]. The persistence of negative blood culture status even after widespread complications could be owing to the prior use of antibiotics which may be in our case too. Various bacteria like HACEK group, Abiotrophia spp, Brucella spp, Rickettsia spp, Chlamydia spp, Tropheryma whipplei, Bartonella spp, Mycoplasma, Legionella and fungi were implicated in BCNE[7,9] among which many fastidious organisms could now be routinely identified with modern blood-culture techniques and specialized media. Staphylococcal and streptococcal species can be the major underlying cause of BCNE in patients who have received antibiotics before the blood culture[10]. Fungal causes have also been identified as a common cause of nosocomial BCNE in postoperative cases[11]. Though uncommon, inflammatory diseases like SLE and Behcet's disease can be associated with BCNE[10].

Both diagnostic and therapeutic approaches towards BCNE can be a demanding task for a physician. A thorough and well-detailed history, clinical examination, special culture techniques, molecular techniques, and histopathological evaluation of valvular tissue whenever appropriate, are crucial towards diagnosis. A meticulously elicited history alone can serve as an essential clue. Hence, the underlying immune status of the patient, consumption of unpasteurized milk and milk products, and contact with domestic and farm animals (suspecting underlying Coxiella infection) should be elicited. Similarly, risk factors associated

with Bartonella infection such as homelessness, chronic alcoholism, and contact with human body lice should also be part of assesment[12,13]. The presence of concurrent joint, digestive, and neurological symptoms point towards Tropheryma whipplei[14]. Risk factors for underlying fungal infections like intravenous drug use, parenteral nutrition, and active cancer should also be considered[10]. Likewise, travel history, history of antibiotics usage, lab exposure to pathogens, etc. can provide important clue to the underlying causes. The role of Duke's criteria in the diagnosis of infective endocarditis in such circumstances is suboptimal[15]. The role of PCR in the diagnosis of BCNE has also been well described in the literature[12,16]. Transthoracic and transesophageal echo can be useful in both diagnosis as well as prognosis. The diagnostic complexity leading to delays may result in complications from BCNE including embolization to the lung, spleen, and brain[17].

Currently, empirical antibiotic therapy is recommended for BCNE[18]. A multidisciplinary approach involving Internist, infectious disease specialist, cardiologist, and microbiologist is often needed. Infectious disease specialist consultation is recommended before initiating antibiotics therapy. Coverage for Staphylococcus aureus, Beta haemolytic streptococci, and aerobic Gram-negative bacilli with vancomycin and cefepime as the first-line regimen in acute cases[2,19]. Subacute cases require additional coverage for streptococci, and enterococci with Vancomycin and ampicillin-sulbactam. HACEK Gram-negative bacilli require third-generation cephalosporin and quinolones while Aspergillus usually responds to voriconazole. Surgical therapy during the active phase of the disease is associated with significant risk. Surgery is justified in patients with high-risk features that make the possibility of a cure which is unlikely with antibiotic treatment[19].

In our case, the patient had a persistent infection in the form of growing mitral valve vegetation. Despite broad-spectrum IV antibiotic coverage—Meropenem, Vancomycin, and Bactrim, newly identified foci in the form of vertebral discitis were identified. Overall assessment and investigation of the case indicated the presence of a fastidious organism causing infective endocarditis complicating as brain abscess, solid organ abscess including spleen, liver, and vertebral osteomyelitis with negative serial culture and PCR assay. Prolonged therapy after upgrading to an alternative broad-spectrum proved to be advantageous as the patient showed clinical improvement and the vegetation had also resolved.

Conclusion

In the absence of positive blood culture which is a major diagnostic criterion to establish infective endocarditis, it is diagnostically and therapeutically challenging to treat patients. Patients may have persistent negative cultures due to previous antibiotic use, the presence of fastidious organisms, or inappropriate techniques or media. Involvement of a multidisciplinary team, use of multimodal investigation, and appropriate antibiotic stewardship are crucial. Extended duration of treatment and upgrading antibiotics can be helpful next steps in highly suspicious cases. With multifocal spread as in our case, it further becomes challenging to control and treat the infection as it is frequently connected with higher morbidity and mortality.

Ethical approval

Not Applicable.

Consent

Written informed consent was obtained from the patient for publication and images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

S.L., K.P. and N.B.P. were involved in writing original draft. B.L., S.D. and S.K.A. were involved in conceptualization, design and preparation of manuscript. S.L., B.L., S.D. and S.K.A. were involved in critical review and finalization of manuscript.

Conflicts of interest disclosure

There are no conflicts of interest.

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Data availability statement

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References

[1] Raoult D, Casalta JP, Richet H, *et al*. Contribution of systematic serological testing in diagnosis of infective endocarditis. J Clin Microbiol 2005;43:5238–42.
[2] Ebato M. Blood Culture-Negative EndocarditisFirstenberg MS, ed. Advanced Concepts in Endocarditis. InTech; 2018.
[3] Werner M, Andersson R, Olaison L, *et al*. A clinical study of culture-negative endocarditis. Medicine 2003;82:263–73.
[4] Lamas CC, Eykyn SJ. Suggested Modifications to the Duke Criteria for the Clinical Diagnosis of Native Valve and Prosthetic Valve Endocarditis: Analysis of 118 Pathologically Proven Cases. Clin Infect Dis 1997;25:713–9.
[5] Kupferwasser LI, Bayer AS. Kulturnegative endokarditis: ätiologie, diagnostik, management und therapie. Herz 2001;26:398–408.
[6] Agha RA, Franchi T, Sohrabi C, *et al*. The SCARE 2020 Guideline: Updating Consensus Surgical CAse REport (SCARE) Guidelines. Int J Surg 2020;84:226–30.
[7] Brouqui P, Raoult D. Endocarditis due to rare and fastidious bacteria. Clin Microbiol Rev 2001;14:177–207.

[8] Lamas CC, Fournier PE, Zappa M, *et al*. Diagnosis of blood culture-negative endocarditis and clinical comparison between blood culture-negative and blood culture-positive cases. Infection 2016;44: 459–66.
[9] Lamas CC. Blood culture negative endocarditis: analysis of 63 cases presenting over 25 years. Heart 2003;89:258–62.
[10] Tattevin P, Watt G, Revest M, *et al*. Update on blood culture-negative endocarditis. Med Mal Infect 2015;45:1–8.
[11] Thuny F, Fournier PE, Casalta JP, *et al*. Investigation of blood culture-negative early prosthetic valve endocarditis reveals high prevalence of fungi. Heart 2010;96:743–7.
[12] Houpikian P, Raoult D. Blood culture-negative endocarditis in a reference center. Medicine 2005;84:162–73.
[13] Roux V, Raoult D. Body lice as tools for diagnosis and surveillance of reemerging diseases. J Clin Microbiol 1999;37:596–9.
[14] Fenollar F, Célard M, Lagier JC, *et al*. Tropheryma whipplei Endocarditis. Emerg Infect Dis 2013;19:1721–30.
[15] Shahani L. Culture negative endocarditis: a diagnostic and therapeutic challenge!. Case Rep 2011;2011(nov08 1):bcr0720114538–.
[16] Anton-Vazquez V, Dworakowski R, Cannata A, *et al*. 16S rDNA PCR for the aetiological diagnosis of culture-negative infective endocarditis. Infection 2022;50:243–9.
[17] Thuny F, Disalvo G, Belliard O, *et al*. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography. Circulation 2005;112:69–75.
[18] Habib G, Lancellotti P, Antunes MJ, *et al*. 2015 ESC Guidelines for the management of infective endocarditis. Eur Heart J 2015;36:3075–128.
[19] Baddour LM, Wilson WR, Bayer AS, *et al*. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. Circulation 2015;132:1435–86.