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Navigating diagnostic challenges in *Bartonella*-induced infective endocarditis: a case report

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Abstract

Background Blood culture-negative infective endocarditis presents a significant clinical and diagnostic challenge owing to its atypical presentation and difficulty in identifying causative pathogens. *Bartonella henselae*, a rare cause of blood culture-negative infective endocarditis, can further complicate its diagnosis and treatment.

Case presentation This case report describes the intricate diagnostic journey and therapeutic challenges encountered in a 65-year-old Tunisian female diagnosed with *Bartonella henselae*-induced infective endocarditis. The patient presented with symptoms of general weakness, weight loss, arthralgia, and a 2-month history of fever along with hepatic involvement characterized by cholestasis and portal hypertension. Despite initial empirical antibiotic therapy leading to temporary improvement, the patient experienced relapse, prompting further investigation. Positive serological tests for *Bartonella henselae* guided the initiation of targeted antibiotic therapy with rifampin and doxycycline, which resulted in significant clinical improvement. However, the subsequent acute pulmonary edema revealed severe triple-vessel coronary disease, necessitating aortic valve replacement surgery and coronary artery bypass grafting. The patient recovered well postoperatively, with cultures from the aortic valve confirming *Bartonella henselae* infection.

Conclusions This report underscores the importance of heightened awareness, comprehensive diagnostic imaging, and careful consideration of treatment strategies in patients with atypical infective endocarditis. This highlights the need for the early suspicion and identification of Bartonella henselae in BCNIE cases, particularly in patients with relevant epidemiological exposure.

Keywords Culture negative endocarditis, Bartonella endocarditis, Aortic valve vegetation, Case report

Background

Infective endocarditis (IE) is a life-threatening, systemic infectious disease. Its high morbidity and mortality rate make it a significant public health concern [1]

Antibiotic resistance is a major factor in the increase in the population at risk for IE. In addition, a significant factor in the increase in IE incidence is the emergence of new diagnostic tools and multimodal imaging for IE diagnosis. A number of conditions are typically essential to placing this group at risk, including the existence of predisposing risk factors, particularly for individuals with congenital heart disease, prosthetic valves, or any intracardiac material. The diagnosis of IE is established according to the modified Duke criteria [2].

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Identification of microorganisms by blood culture is initially a cornerstone for diagnosis and treatment. In some cases, if blood culture is negative, empirical therapy is started with further investigation, and blood culture-negative infective endocarditis accounts for 5–10% of all cases of endocarditis.

BCNIE is often severe and difficult to diagnose [3]. Three primary categories identify blood culture-negative infective endocarditis (BCNIE): endocarditis caused by fastidious microorganisms requiring extended incubation, bacterial endocarditis with blood cultures sterilized by prior antibiotic therapy, and true blood culture-negative endocarditis as a result of intracellular bacteria that are not routinely cultured in blood [4].

The main causes of BCNIE are *Brucella* spp., *Coxiella burnetii*, *Bartonella* spp., *Legionella* spp., *Mycoplasma* spp., and *Tropheryma whipplei*.

A team approach is needed for the diagnosis and treatment of blood culture-negative endocarditis because it requires sophisticated and innovative molecular analysis, histology, and vital epidemiological information.

Molecular and serological techniques have emerged as crucial tools for *Bartonella* species detection. The most common species among the 14 species associated with *Bartonella* endocarditis was *B. henselae*. Catch-scratch illnesses are also recognized to be mostly caused by this species [5].

Bartonella henselae endocarditis is a rare but serious condition, with a limited number of cases reported in the literature. This rarity makes diagnosis challenging and often leads to delays and complications. The atypical presentation of *Bartonella* endocarditis, particularly in populations without common risk factors, further complicates its diagnosis. There is a specific knowledge gap regarding the diverse clinical manifestations and optimal management strategies for *Bartonella* endocarditis, especially in patients without a clear epidemiological history of animal exposure. Addressing these knowledge gaps is crucial for improving the diagnostic accuracy and treatment outcomes in affected patients.

The aim of this report was to present a case of *B. henselae* endocarditis associated with *Bartonella*-infected domestic animals in Tunisia, highlighting the diagnostic challenges and therapeutic strategies involved.

Case description

A 65-year-old Tunisian woman presented to our department in July 2023 with general weakness, weight loss, arthralgia, and symmetrical petechial and purpuric rashes on her feet. The patient reported a 2-month history of fever. Her medical history included type 2 diabetes for the past 5 years, which was effectively managed. Additionally, the patient had hypothyroidism and was currently receiving levothyroxine. She also had dyslipidemia. In 2021, the patient underwent coronary stenting for a non-ST-elevation myocardial infarction. Echocardiography revealed a preserved left ventricular ejection fraction and no valvular heart disease. Additionally, 3 months before the present admission, the patient underwent evaluation by a gastroenterologist for thrombocytopenia and anicteric cholestasis. Clinical manifestations indicative of portal hypertension such as moderate ascites and splenomegaly were also observed. Serological tests for hepatitis B and hepatitis C yielded negative results. Abdominal ultrasound results supported the diagnosis, demonstrating characteristics aligned with portal hypertension and cirrhosis classified as stage F3–F4 according to FibroScan analysis. On admission, the patient presented with a body temperature of 38.1 °C. Vascular ecchymotic purpura were observed in the lower limbs. Cardiovascular examination revealed no abnormalities and palpation revealed splenomegaly. Echocardiography revealed a preserved left ventricular ejection fraction with no wall motion abnormalities. The aortic valve was tricuspid and showed a mobile image measuring 4 mm × 9 mm on the non-coronary cusp and prolapsing into the left ventricular outflow tract, causing grade 2 aortic insufficiency, with a vena contracta of 4 mm (Figs. 1, 2).

The initial biochemical profile of the patient revealed anemia with a hemoglobin level of 9 g/dL, platelet count of 175,000/mm^3, and white blood cell count of 6030/

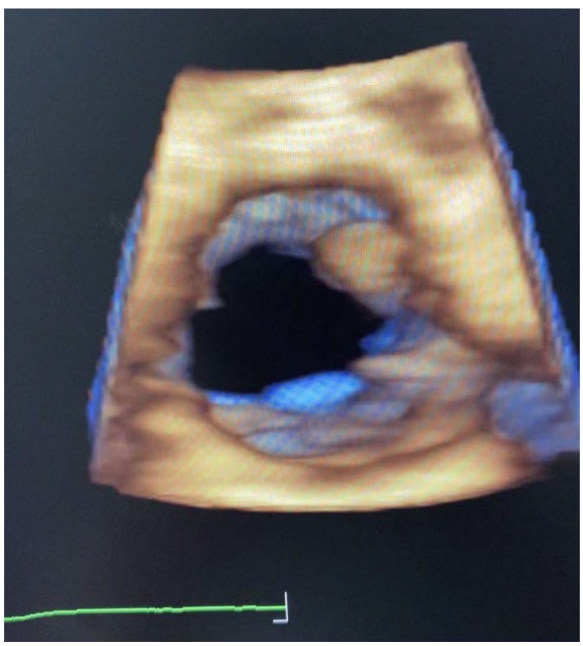

Fig. 1 The aortic valve vegetation on three-dimensional (3D) echocardiography

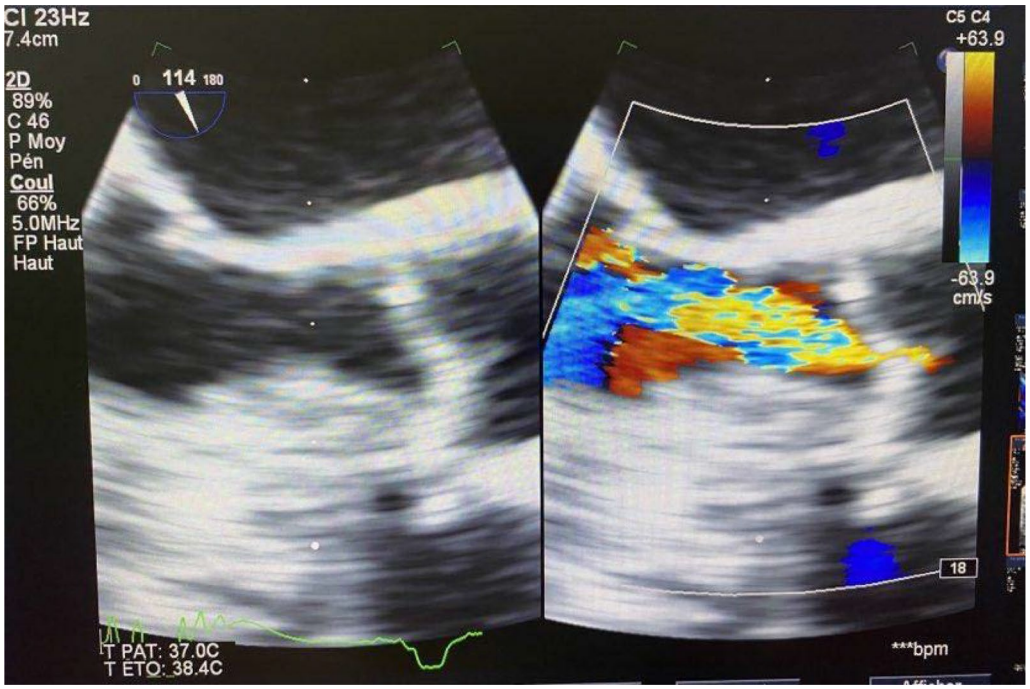

Fig. 2 Two-dimensional (2D) transesophageal echocardiography showing grade 2 aortic valve regurgitation

mm^3. Renal function parameters were as follows: urea, 8.48 mmol/L and creatinine, 115 µmol/L. Inflammatory marker levels were elevated, with a C-reactive protein level of 41 mg/L. Liver function tests revealed mild abnormalities, including aspartate aminotransferase (ASAT) at 43 U/L, alanine aminotransferase (ALAT) at 14 U/L, and gamma-glutamyl transferase (GGT) at 175 U/L. Alkaline phosphatase (PAL) were notably elevated at 348 U/L. The immunological profile was negative for antineutrophil cytoplasmic antibodies (ANCA), anti-extractable nuclear antigens (ENA), and anti-mitochondrial antibodies (anti-ML).Additionally, the rheumatoid factor (RF) level was elevated, exceeding 200 IU/mL, whereas anti-cyclic citrullinated peptide (anti-CCP) and anti-fibrillarin antibodies (anti-FI) were both negative. Urinary analysis revealed a 24 hour protein excretion of 0.2 g/24 hour, with no detectable hematuria or red blood cell casts. A skin biopsy revealed characteristics indicative of leukocytoclastic vasculitis, with medium-intensity C3 and IgM deposits detected in the vascular structures. In the presence of signs of infective endocarditis, despite negative blood cultures and a thoracoabdominopelvic computed tomography (CT) scan showing no abnormalities, empirical antibiotic therapy was initiated. The chosen treatment regimen included ampicillin, oxacillin, and gentamicin, with dosages tailored to the results of blood analyses. After 10 days of antibiotic therapy, there was an initial improvement in the apyrexia and a decrease in the levels of biological inflammatory markers. However, febrile episodes recurred and C-reactive protein levels increased, indicating an incomplete response to the initial treatment. Antibiotic therapy was modified without improvement, and investigation of the rare causes of culture-negative endocarditis was initiated. Serological tests for *Coxiella burnetii*, *Legionellosis*, *Aspergillus*, *Mycoplasma*, *Tropheryma whipplei*, and brucellosis all returned negative results. In addition, a positron emission tomography (PET) scan was performed and the results were negative. On day 14, serological tests for *Bartonella henselae* were positive and both IgM and IgG were positive. Antibiotic treatment with rifampin and doxycycline was initiated; however, aminoglycosides were not incorporated into the treatment regimen because of the patient's borderline kidney function. At this point, the patient recalled being scratched by a cat several months prior to her current admission. The patient showed significant improvement with this treatment, with complete resolution of fever, normalization of inflammatory markers, stability of cardiac ultrasound findings, and restoration of liver function values to normal levels. One month later, the patient presented with acute pulmonary edema without evident etiology. Coronary angiography was performed to assess the coronary status, revealing triple-vessel disease with involvement of the left main coronary artery. Echocardiography revealed the same appearance of vegetation responsible for grade 2

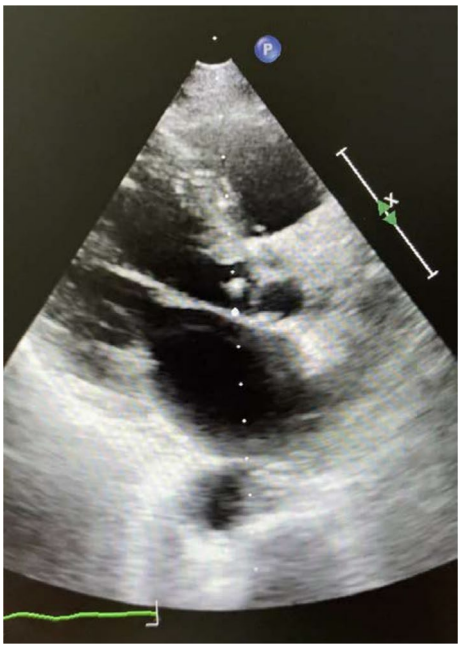

Fig. 3 Two-dimensional (2D) echocardiography,Long axis, mobile aortic valve vegetation

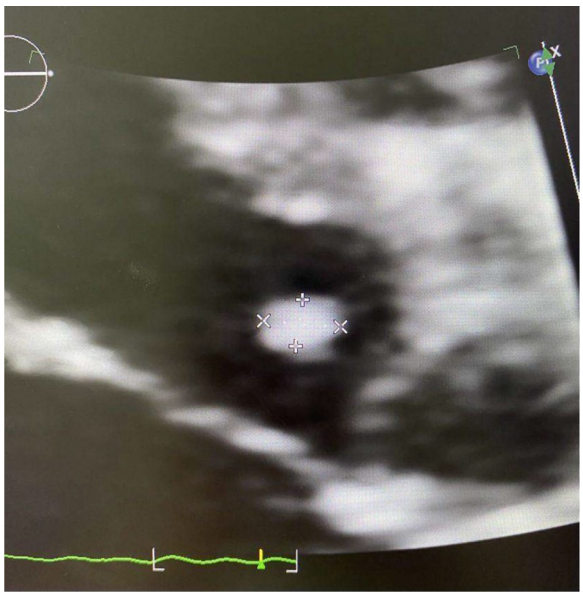

Fig. 4 Two dimenisonal (2D) echocardiography. A 0.9 cm × 0.4 cm mobile aortic valve vegetation

aortic valve regurgitation (Figs. 3, 4). Given this condition and the low operative risk in our patient, we decided to proceed with aortic valve replacement using a mechanical prosthesis and coronary artery bypass grafting. The patient underwent surgery with good postoperative recovery, and the culture of the aortic valve was positive for *Bartonella henselae*, which further supports our diagnosis.After the surgery, the patient was closely monitored with monthly follow-up visits. Throughout this period, she demonstrated a favorable clinical course, remaining apyretic with a preserved general condition. Monthly transthoracic echocardiograms consistently showed a good hemodynamic profile of the aortic prosthesis with no evidence of vegetation. Now, 1-year post-surgery, she continues to undergo regular follow-ups, maintaining a stable recovery and showing no signs of complications.

Discussion and conclusions

Bartonella henselae infective endocarditis poses a diagnostic challenge in predisposed patients and is associated with a high mortality rate. A substantial level of suspicion is needed for early identification because atypical presentations and lack of usual signs and symptoms of infection can delay diagnosis. When blood cultures are negative after 72–96 hours, individuals with epidemiological risk factors should be evaluated for the disease [6].

Bartonella henselae is an intracellular pathogen that primarily infects the endothelial cells and macrophages. After entering the host, often through a scratch or bite from an infected cat, the bacteria disseminate through the bloodstream and adhere to the damaged endocardial surfaces. The bacteria's ability to invade endothelial cells and evade the host immune response is a key factor in its pathogenicity. Chronic infection of endothelial cells leads to the formation of vegetation on heart valves, which are aggregates of platelets, fibrin, and bacteria. These vegetation types can cause valve dysfunction, embolic phenomena, and systemic inflammatory responses. The fastidious nature of *Bartonella henselae*, which requires specific culture conditions and extended incubation periods, complicates its detection in blood cultures, often necessitating the use of serological and molecular diagnostic techniques.

Culture-negative endocarditis is associated with several *Bartonella* species. Up to 95% of cases are accounted for with two common species: *B. henselae* and *B. Quintana* [7]. Patients with negative blood cultures and risk factors for these infections should consider early serological testing. Polymerase chain reaction (PCR) has a 100% specificity rate but only a 58% sensitivity, and the test is not always accessible. In addition, the fastidious nature of the organism limits its growth in blood cultures, and the incubation period can extend up to 21 days, which further delays prompt identification and treatment. Therefore, the initial diagnosis is reliant on the evaluation of serum IgM and IgG titers [8].

In our case report, the classification of endocarditis according to the Duke criteria underscores the diagnostic uncertainty initially encountered [9]. Given the

urgency of the situation, empirical antibiotic therapy was promptly initiated while awaiting specific test results. This proactive approach facilitates early treatment initiation and contributes to the initial stabilization of the patient. Furthermore, comprehensive patient interrogation revealed crucial information regarding exposure to kittens, prompting suspicion of *Bartonella henselae* infection. This highlights the importance of thorough history-taking to guide the diagnosis of specific pathogens and prevent treatment delays. The timely recognition of *Bartonella henselae* infection allowed for swift adjustment of antibiotic therapy, replacing empirical treatment with a tailored combination targeting the identified pathogen. This not only enhanced treatment efficacy but also reduced the risk of complications, leading to improved patient outcomes.

The long-term prognosis of patients with *Bartonella* endocarditis who undergo successful surgical intervention and appropriate antibiotic therapy is generally favorable. In our case, the patient's condition improved significantly after valve replacement surgery and targeted antibiotic treatment, and no recurrence of infection was observed during follow-up.

Our case underscores the critical importance of an integrated approach in managing patients with infective endocarditis, emphasizing the significance of accurate classification, prompt initiation of empirical therapy, and thorough interrogation to guide diagnosis and optimize therapeutic outcomes.

However, a major challenge is the time-consuming nature of these diagnostic methods, and the difficulty of determining the appropriate treatment for individuals with infective endocarditis that is culture-negative [10]. It is essential to establish a balance between the necessity of empirical antibiotic therapy and the possible toxicity of certain drugs, including aminoglycosides [11].

A more thorough investigation into the causes of culture-negative endocarditis, incorporating history, physical examination, and additional diagnostic tools are necessary in cases of negative blood cultures, which pose a diagnostic issue. Health professionals should be alert to an atypical case of infective endocarditis, especially when patients have weight loss, manifestation of liver damage, and epidemiological history of domestic animals.

The limitations of this case report include its limited generalizability.While the case provides valuable insights into the diagnosis and management of *Bartonella* endocarditis, the specific clinical presentation and treatment approach may not be applicable to all patients. Each case of endocarditis can present uniquely, especially in the context of culture-negative infections, which underscores the need for individualized patient assessment and management. Future investigations should balance empirical therapy with potential drug toxicities, particularly with aminoglycosides. *Bartonella* endocarditis requires high clinical suspicion, especially weight loss, liver damage, and contact with domestic animals.

Abbreviations

IE	Infective endocarditis
BCNIE	Blood culture-negative infective endocarditis
CRP	C-reactive protein
ASAT	Aspartate aminotransferase
ALAT	Alanine aminotransferase
GGT	Gamma-glutamyl transferase
PAL	Alkaline phosphatase
ANCA	Antineutrophil cytoplasmic antibodies
ENA	Anti-extractable nuclear antigens
Anti-ML	Anti-mitochondrial antibodies
RF	Rheumatoid factor
Anti-CCP	Anti-cyclic citrullinated peptide
Anti-FI	Anti-fibrillarin antibodies
PCR	Polymerase chain reaction

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Author contributions
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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors have no disclosures to report and have no conflict of interest.

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