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Q fever endocarditis: a diagnostic challenge in a complex cardiological case

Riccardo Rovelli, Elisa Brangi, Francesca Capasso,
Martina Mazzini, Michela Raffo, Enrico Vizzardi

Cardiovascular Disease Section, Department of Medical-Surgical Specialty, Radiology and Health Care, School of Medicine, Spedali Civili Hospital, Brescia, Italy

Correspondence: Rovelli Riccardo, Cardiovascular Disease Section, Department of Medical-Surgical Specialty, Radiology and Health Care, School of Medicine, Spedali Civili Hospital, Piazzale Spedali Civili, 1, 25123 Brescia, Italy.
Tel.: 3348266468. E-mail: riccardo.rovelli97@gmail.com

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Abstract

Q fever endocarditis remains a diagnostic challenge today. Although it is a rare condition, it is crucial to recognize, as it represents the most common cause of endocarditis with persistently negative blood cultures. Here, we present the case of a 73-year-old woman with a history of coronary artery disease and systemic sclerosis who was admitted to the hospital complaining of asthenia and dyspnea. An echocardiographic examination revealed a highly mobile pedunculated mass on the mitral valve, suggestive of endocarditis. During the diagnostic workup, blood cultures were repeatedly negative, but serological testing confirmed positivity for *Coxiella burnetii* (IgG phase I 1:128). After diagnosing Q fever endocarditis, antibiotic therapy with doxycycline and hydroxychloroquine was initiated but was soon discontinued due to the development of renal impairment and thrombocytopenia. The clinical course was further complicated by cardiac arrest, leading to the patient's death. Given the rarity of this condition, this case highlights the importance of considering Q fever endocarditis in the differential diagnosis of blood culture-negative endocarditis and underscores the need for rapid diagnosis using advanced diagnostic techniques to improve patient outcomes.

Key words: Q fever, *Coxiella burnetii*, infective endocarditis, blood culture-negative endocarditis, valvular heart disease.

Introduction

Q fever is a zoonosis caused by an obligate intracellular gram-negative bacterium: Coxiella Burnetii. It is an infection that predominantly occurs in subjects who have contact with domestic or wild animals and live mainly in rural settings [1,2].

There are two main forms of Q fever: the acute form, which in 60% of cases is asymptomatic and in the remaining number of cases manifests itself mainly as a nonspecific fever, associated with acute hepatitis or atypical pneumonia; and the chronic form, which develops in approximately 5% of patients, particularly in those with a history of valvular disease, in immunocompromised subjects and in pregnant women. The chronic form manifests itself mainly in the form of endocarditis with persistently negative blood cultures [3], making it the most common cause of blood culture negative endocarditis (BCNE) [4].

The 2023 Duke-ISCVID Criteria for infective endocarditis outline that Q fever endocarditis can be diagnosed when either Coxiella burnetii is identified by polymerase chain reaction (PCR) or when the phase I IgG antibody titer exceeds 1:800, alongside characteristic echocardiographic findings [5].

In clinical practice, the condition's insidious nature and the nonspecific symptoms associated with chronic infections often delay diagnosis, increasing the risk of adverse outcomes.

Here, we present a case of Q fever endocarditis in a complex patient with significant comorbidities, highlighting the diagnostic difficulties and therapeutic decisions made during this clinical case.

Case Report

A 73-year-old Caucasian woman with a history of hypertension, diabetes, atrial fibrillation in oral anticoagulant therapy, dyslipidemia, chronic ischemic heart disease following percutaneous coronary intervention with drug-eluting stent placement in the left anterior descending artery (2014), valvular heart disease, and systemic sclerosis (Scl70+), resulting in secondary interstitial lung disease and pulmonary hypertension, presented to the Don Gnocchi Center in Brescia for respiratory rehabilitation in April 2024. At that time, the patient was afebrile, but complained of asthenia and dyspnea on exertion, consistent with NYHA class II heart failure symptoms.

Echocardiographic evaluation revealed the presence of a large, mobile, pedunculated mass at the level of the posterior mitral leaflet, suspicious for infective endocarditis. In light of this finding, the patient was immediately transferred to ASST Spedali Civili in Brescia and underwent blood cultures, which were initially negative. At the subsequent echocardiogram, the presence of the multilobulated, mobile mass (20 mm x 11 mm) at the level of the posterior

mitral leaflet was confirmed; furthermore, in this examination the presence of moderate mitral stenosis and pulmonary hypertension (PAPs 85 mmHg) were reported (Figures 1 and 2).

The case was discussed collegially with infectious disease colleagues and, in consideration of the possible diagnosis of endocarditis and the high embolic risk of the lesion, it was agreed to start empirical antibiotic therapy with Oxacillin, Ampicillin and Gentamicin. This empirical regimen was chosen in line with ESC guidelines for native valve infective endocarditis [6], considering the high initial suspicion for staphylococcal or enterococcal etiology in a high-risk patient.

In order to exclude systemic embolization, the patient underwent a brain CT scan, which was negative, and a chest-abdomen CT scan, which was negative, but identified progression of the patient's known fibrosing interstitial lung disease.

Cardiac MRI was not performed due to the patient’s progressive clinical deterioration, which made advanced imaging techniques unfeasible during hospitalization.

To complete the diagnostic assessment, blood cultures were repeated, which were again negative; skin, nasal and rectal swabs were carried out for sentinel germs, resulted negative, and serological tests for atypical bacteria were done, with positive findings for anti-Coxiella Burnetii IgG.

Given the feedback, further serological samples were sent to the ASST Cremona laboratory to define the antibody titer and the positivity for anti C. Burnetii IgG was confirmed: phase I antigen had a titer of 1:128 and phase II antigen had a titer of 1:256, which supported the strong suspicion of Q fever endocarditis. Therefore the antibiotic therapy was modified, with initiation of specific therapy for Q fever with doxycycline and hydroxychloroquine.

The case wasn’t discussed with the cardiac surgery team, due to the patient’s fraility, severe comorbidities, and rapid clinical deterioration, which rendered surgery not feasible, so we decided to treat the patient only with antibiotic therapy.

During the subsequent hospital stay the patient's condition deteriorated with progressive renal impairment and thrombocytopenia, leading to the discontinuation of hydroxychloroquine. The course was further complicated by gastrointestinal bleeding, requiring suspension of anticoagulant therapy and blood transfusions due to anemization.

Despite the initiation of appropriate treatment, repeat echocardiography one month later demonstrated the persistence of the vegetation, unchanged in size. The patient's clinical condition continued to decline, with multiple episodes of psychomotor agitation and loss of consciousness. Two weeks after the start of specific therapy, the patient experienced a sudden cardiopulmonary arrest, with failed resuscitation efforts leading to her death. Although the exact cause of death could not be confirmed due to the absence of post-mortem examination,

a fatal arrhythmic event or systemic embolization event from the large mitral vegetation was strongly suspected. Other causes, including sepsis, could not be ruled out.

Discussion

Q fever endocarditis still represents a significant diagnostic challenge; mainly because of the difficulty of growth of C. Burnetii on standard culture media and because of the atypical clinical presentation. Valvular vegetations, typical of endocarditis, are often small in size, making them difficult to identify on echocardiography. Furthermore, the absence of specific symptoms of the infection complicates the picture, often leading to a delay in diagnosis and a consequent increase in the risk of death [7].

The clinical manifestations of Q fever endocarditis are nonspecific and patients may be asymptomatic or present relapsing fever, chills, night sweats, weight loss, and hepatosplenomegaly [8]. Sudden cardiac insufficiency, stroke, or other embolic signs are also presentations of the disease [7]. The main alterations found on laboratory tests are hyperleukocytosis or pancytopenia [9,10].

In the case of our patient, in particular, the absence of fever and repeated initially negative blood cultures complicated the diagnostic process. This presentation, however, is typical of Q fever endocarditis; in fact, studies in the literature underline that Q fever endocarditis represents the first cause of blood culture-negative endocarditis (BCNE) [3,4].

To improve the chances of diagnosing forms of endocarditis due to C. Burnetii infections, new diagnostic techniques have been proposed; in particular, Lin et al. (2023) [4], underline that the use of molecular techniques, such as PCR for C. Burnetii or serological techniques, looking for antibodies against C. Burnetti represent important tools to reach the diagnosis in the case of blood culture-negative endocarditis.

In particular, IgG I titer of 1:800 is associated with a positive predictive value for endocarditis of 37%, which rises to 75% for IgG I titer of 1:6400 [11].

Although the classical diagnostic threshold for Q fever endocarditis is an IgG phase I titer greater than 1:800, cases with lower titers have been reported in the literature. Edouard et al. (2013) [12] described how patients with low antibody titers may still present with active endocarditis, especially in the context of immunosuppression or valvulopathy.

The diagnostic delay in our case can be attributed to the insidious nature of the disease and the rarity of the pathology. Furthermore, the presence of initially negative blood cultures determined a significant delay in starting the correct antibiotic therapy, implemented only following the serological findings, thus contributing to the unfavorable outcome of the patient.

As underlined by recent guidelines, the use of advanced imaging techniques, such as 18F-FDG PET-CT, represent a further tool to increase the possibility of identifying the infection at an

early stage, especially in patients with slow-evolving infections [13]. In this case, PET-CT was not performed due to the patient's critical condition and logistical limitations.

Q fever is spread worldwide, with a variable geographic distribution; however, the epidemiological characteristics of this disease vary according to the different geographical area considered; thus distinguishing situations in which the infection is endemic, hyperendemic, or less frequently epidemic [14].

Epidemiological studies have shown that men are more frequently affected than women, with a male-to-female ratio of 2.5:1; additional risk factors include age [15], pregnancy, and pre-existing valvular diseases, particularly congenital malformations such as bicuspid aortic valve [16].

In our case, the patient lived in a rural area of northern Italy, however in a region not considered endemic, which contributed to the delayed diagnosis.

The most frequent form of transmission of the infection to humans is due to inhalation of aerosols containing the pathogen, especially those formed from placental derivatives. Wild animals, domestic animals, and ticks are the main reservoirs [17].

When untreated, Q fever endocarditis is associated with a high risk of mortality, which persists even in properly treated patients. Longitudinal studies have shown that, even if treated, the 5-year mortality rate of patients with Q fever endocarditis reaches 10% [7,18]. A study by Million et al. (2010) further emphasizes that, despite adequate therapy, the long-term outcome is poor, with a high risk of mortality due to embolic complications and worsening of heart failure [7].

The ideal treatment for this condition is a combination of doxycycline and hydroxychloroquine, which should be continued for long periods; 18 months for patients with native valves and up to 24 months for those with prosthetic valves [14]. Recent evidence, including the review by Jaltotage et al. [19], suggests that this combination significantly reduces mortality compared to other antibiotic regimens. The synergistic intracellular action of these drugs is considered essential for effective bacterial clearance and prevention of relapses and to improve long term outcomes.

To improve the outcome of patients with Q fever endocarditis, a multidisciplinary approach, including cardiologists, infectious disease specialists and cardiac surgeons, becomes essential; especially in cases where surgery may be considered to remove vegetation or perform a replacement of the affected valve.

In summary, the case presented clearly demonstrates the importance of early diagnosis and prompt treatment in patients with suspected Q fever endocarditis. Although significant progress has been made in managing this infection through new diagnostic and therapeutic tools, the mortality associated with this condition remains high, particularly in patients with pre-existing risk factors.

As a result, it is useful to perform an echocardiogram in all patients with suspected Q fever endocarditis, to identify any valvular alterations and start specific antibiotic treatment as soon as possible [20].

Conclusions

Since Q fever endocarditis is a form of infection that is difficult to diagnose with a high mortality rate, often affecting individuals with known predisposing factors, it becomes essential, in the suspicion of this infection, to carry out an accurate initial screening through imaging tests and serological tests to exclude this condition.

If a form of Q fever endocarditis is identified, it is essential to establish an adequate antibiotic treatment with hydroxychloroquine and doxycycline which must be continued for a long time, with adequate echocardiographic follow-up of the patient, until complete recovery.

Given the high mortality of this clinical condition, early recognition of suspected cases and a multidicplinary approach remain essential in order to improve the prognosis of affected patients.

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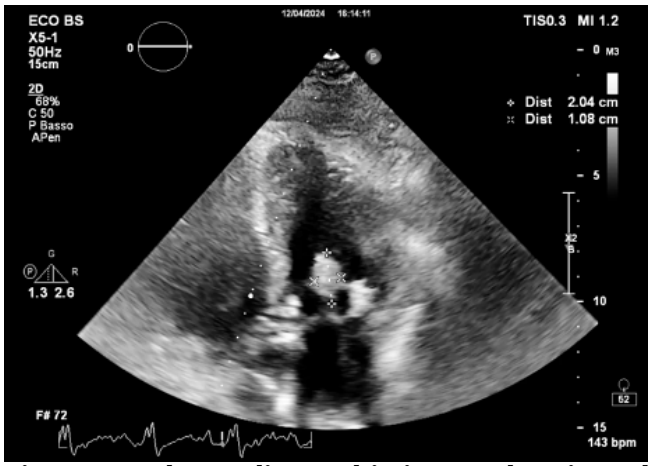

Figure 1. Echocardiographic image showing a large, highly mobile, pedunculated, multilobed mass (length 20 mm, thickness 11 mm), adherent to the mitral annulus in the posteromedial commissural region, four chamber view.

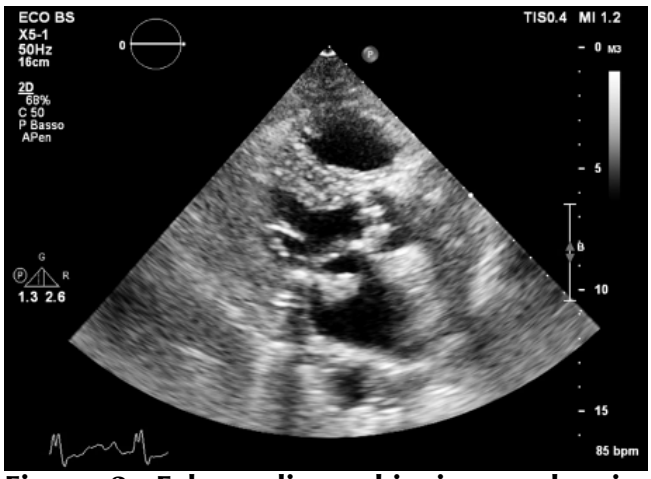

Figure 2. Echocardiographic image showing the same pedunculated, multilobed mass, parasternal long axis view.