CASE REPORT

Q fever endocarditis: is it always subacute or chronic?

Q ateşi endokarditi: Her zaman subakut veya kronik seyirli midir?

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Summary– Q fever is a zoonotic disease caused by *Coxiella burnetii*, an obligate intracellular bacterium, which cannot be grown using routine blood culture methods. Although *C. burnetii* is reported to be the causative agent in approximately 50% of blood culture-negative infective endocarditis cases in developed countries, the incidence in Turkey is yet to be defined. The clinical course of Q fever endocarditis is generally subacute and chronic; the disease may be present for years with only subtle symptoms and no vegetation visible on echocardiography while the bacteria gradually destroy the heart valves. This is the case of the successful treatment of a young man with Q fever endocarditis that had an acute clinical course. In 1 month, he developed New York Heart Association class IV heart failure and a large, 3-cm vegetation was observed on an echocardiogram.

Özet– Q ateşi, zorunlu bir hücre-içi bakterisi olan ve normal kan kültürü şişelerinde üretilemeyen *Coxiella burnetii*'nin neden olduğu zoonotik bir hastalıktır. *C. burnetii*, gelişmiş ülkelerde kan kültürü negatif enfektif endokardit olgularının yaklaşık %50'sinde etken olarak tanımlanırken, ülkemizde bu enfeksiyonlardaki rolü konusunda çok veri yoktur. Q ateşi endokarditi genellikle subakut veya kronik bir seyir gösterir, hastalık çok hafif semptomlarla yıllarca sürebilir, bakteri yavaş yavaş kalp kapağına hasar verirken ekokardiyografide vejetasyon görülmeyebilir. Bu olguda, sadece bir aylık konstitusyonel semptomlardan sonra gelişen NYHA sınıf IV kalp yetersizliği ile prezente olan genç bir erkek hastanın ekokardiyografisinde 3 cm'lik dev bir vejetasyon saptanan akut seyirli bir Q ateşi endokarditi sunulmuştur.

Blood-culture negative endocarditis (BCNE) accounts for up to 35% of all cases of infective endocarditis (IE), and is a serious life-threatening condition with considerable morbidity and mortality.[1] Although *C. burnetii* is reported to be the causative agent in approximately 50% of BCNE cases in developed countries, the role in Turkey is yet to be defined. *C. burnetii* is a zoonotic (primarily sheep, goats, and cows), obligate intracellular bacterium, which cannot be cultured in routine blood culture bottles. Acute Q fever often presents as a nonspecific febrile disease that can occur in conjunction with hepatitis or pneumonia. However, persistent infection commonly manifests as endocarditis, particularly in patients with preexisting native valve disease and those with a prosthetic valve.[2] The clinical course of Q fever endocarditis is generally subacute and chronic; the disease may be present for years with only subtle symptoms. There is often no vegetation visible on an echocardiogram while the bacteria gradually and insidiously continue to destroy the heart valves.

Abbreviations:

BCNE	*Blood-culture negative endocarditis*
HF	*Heart failure*
IE	*Infective endocarditis*
IgG	*Immunoglobulin G*
NT-proBNT	*N-terminal pro-brain natriuretic peptide*
NYHA	*New York Heart Association*
TEE	*Transesophageal echocardiogram*

This report is a description of the diagnosis, management, and 2 years of follow-up of a young man diagnosed with Q fever endocarditis with an acute clinical course.

CASE REPORT

A 35-year-old male presented with a 1-month history of progressive, exertional dyspnea (New York Heart

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Association [NYHA] class IV) and a subfebrile temperature. He had been diagnosed with a bicuspid aortic valve with moderate stenosis and regurgitation in 2011. One month prior to presentation, he had been admitted to the hospital with constitutional symptoms, and moxifloxacin 400 mg/day was prescribed for possible pneumonia. After several days, a generalized skin rash developed, and methylprednisolone 40 mg/day was initiated orally. The skin lesions resolved, but he developed paroxysmal nocturnal dyspnea and orthopnea.

The patient lived in a rural area of Istanbul, Turkey, and had contact with livestock animals, including cows and sheep.

The patient was hospitalized in our institution. He had a temperature of 38°C, a pulse rate of 103 beats/minute, a respiratory rate of 25 breaths/minute, and a blood pressure of 115/60 mmHg. The physical examination revealed ++ pretibial edema with godet leaving on both legs, a 4/6 systolic murmur on all cardiac auscultation sites, a left-sided fourth heart sound, tachypnea, and bibasilar crackles. There were no peripheral signs of endocarditis, such as subconjunctival hemorrhage, Osler's nodes, Janeway lesions, or splinter hemorrhages. Electrocardiogram results were consistent with sinus tachycardia. A chest X-ray demonstrated an increased cardiothoracic ratio and interstitial pulmonary edema with peribronchial cuffing and Kerley lines. A complete blood count revealed severe anemia, with a hemoglobin level of 7.7 g/dL. The white blood cell count and platelet count were normal. The erythrocyte sedimentation rate was 53 mm/hour, and the C-reactive protein level was 33 mg/L. Liver function tests indicated an elevated level of aspartate aminotransferase of 45 U/L, alanine aminotransferase level of 48 U/L, and an alkaline phosphatase level of 117 U/L, with slightly elevated levels of total bilirubin at 1.7 mg/dL and direct bilirubin at 0.7 mg/dL. Additional test results included an N-terminal pro-brain natriuretic peptide (NT-proBNP) value of 7774 pg/mL and a rheumatoid factor of 453 IU/mL. Transthoracic echocardiogram results demonstrated an immobile, hyperechogenic, pedunculated mass on an aortic cusp (Video 1*) moderate aortic stenosis with a mean gradient of 25 mmHg and a peak velocity of 3.25 m/second (Fig. 1), and severe aortic regurgitation, with a pressure half-time of 87 milliseconds (Fig. 2). The left ventricular ejection fraction calculated according to the Simpson method was 70%. Left ventricular hypertrophy, dilatation of all cardiac chambers, severe tricuspid regurgitation, grade II diastolic dysfunction, and severe systolic pulmonary hypertension (estimated systolic pulmonary artery pressure: 65 mmHg) were recorded. The aortic root and the ascending aorta were also dilated, with a maximal diameter of 5.1 cm. A consultation for infectious disease was conducted, and administration of ampicillin-sulbactam 4x3 g/day and vancomycin 2x1 g/day was initiated intravenously. Transesophageal echocardiogram (TEE) was performed to rule out endocarditis, additional cardiac pathologies, and complications. The TEE yielded imaging of a bicuspid aortic valve and an immobile, pedunculated mass with dimensions of 3.1x1.0 cm attached to an aortic cusp that was consistent with vegetation (Fig. 3, 4, Video 2, 3*), with no abscess or fistula formation. Three sets of blood cultures were negative. A Wright test was also

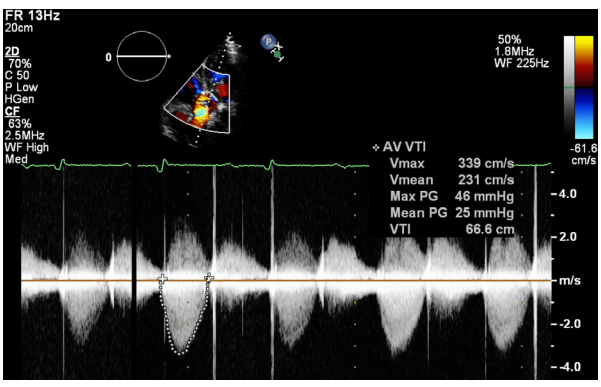

Figure 1. Continuous Doppler flow recording of aortic valve depicting a mean gradient of 25 mmHg, which is consistent with moderate aortic stenosis.

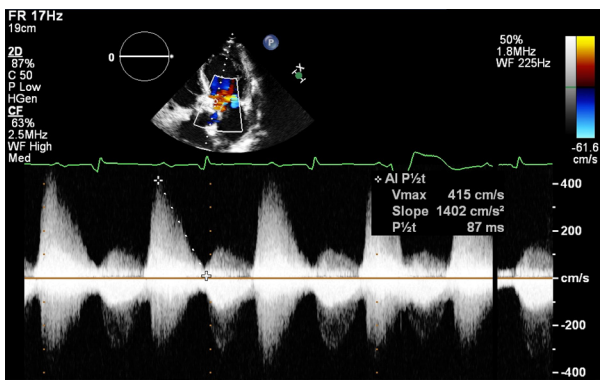

Figure 2. Continuous Doppler flow recording of aortic valve depicting a pressure half-time of 87 ms, consistent with severe aortic regurgitation.

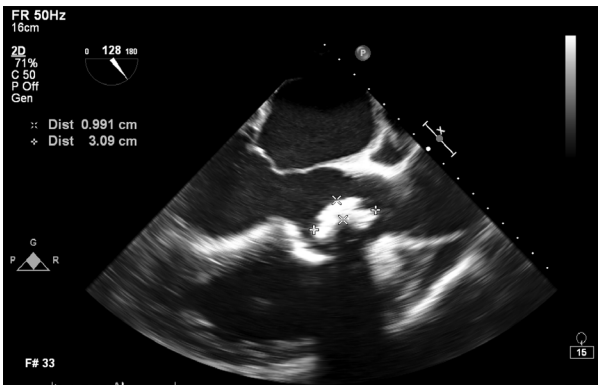

Figure 3. Two-dimensional transesophageal echocardiogram image of the left ventricular long axis demonstrating a large, hyperechogenic, immobile vegetation attached to an aortic cusp.

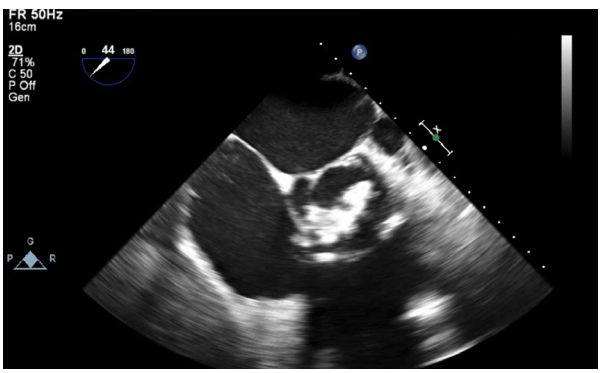

Figure 4. Two-dimensional transesophageal echocardiogram image of the short axis demonstrating the bicuspid aortic valve and a hyperechogenic, immobile vegetation attached to an aortic cusp.

negative. Thorax, abdominal, and cranial computed tomography scans revealed multiple mediastinal and hilar lymphadenopathies and hepatomegaly without any cerebral embolic infarction. *Coxiella* Phase I immunoglobulin G (IgG) antibodies were positive, with a 1:32768 titer. The patient met 2 major and 3 minor modified Duke criteria (first major criterion: *Coxiella burnetii* Phase I IgG >1:800; second major criterion: valve vegetation on cardiac valve; minor criteria: predisposing heart valve disease, fever, and immunological phenomenon [rheumatoid factor positivity]), and a diagnosis of IE was considered definitive. Doxycycline 2x100 mg/day and hydroxychloroquine 3x200 mg/day orally, as well as ciprofloxacin 2x400 mg/day intravenously were initiated. Despite maximal medical therapy, including diuretics and nitrates, surgical aortic valve replacement with a 25-mm Mitroflow bioprosthesis (Sorin Group Italia S.p.a., Milan, Italy) was necessary on the 14th day of hospitalization. After the surgery, the clinical presentation of heart failure (HF) ameliorated in days. He was discharged from the hospital with oral antibiotherapy.

Microbiological examination of heart valve tissue obtained during surgery using polymerase chain reaction revealed *C. burnetii* DNA, and the bacterium was isolated with a cell culture assay (unpublished data).

Treatment with doxycycline and hydroxychloroquine was scheduled to continue for at least 24 months, and follow-up visits were planned for 3-month intervals. The *Coxiella* Phase I IgG titer had fallen to the quarter of the initial titer at the 20th month of treatment, which was assessed as successful treatment. Anemia, liver function, and acute phase response test results had returned to normal levels at the fifth month of treatment.

At the time of writing, postoperative transthoracic echocardiogram images have shown a normally functioning bioprosthetic aortic valve (Videos 4, 5[*]) and normal left ventricular systolic function. At the last follow-up, 24 months after starting treatment, the patient was in good general condition.

DISCUSSION

This case of IE is important due to both the causative agent and the clinical presentation. *C. burnetii* cannot be cultured in routine blood culture bottles, and is the major pathogen of blood-culture negative IE in developed countries. Although there have been acute cases of Q fever and small epidemics in Turkey since 1948, the first case of Q fever endocarditis was reported in 2016. This is the third case report of Q fever endocarditis in our country. All 3 cases were acquired in Turkey and were diagnosed in our hospital.[3,4] These findings highlight the importance of *C. burnetii* in cases of BCNE in general, and in Turkey, in particular. The diagnosis of Q fever endocarditis can be easily made with a serological determination of *Coxiella* Phase I IgG, which is a major Duke criterion when a titer is greater than 1:800. Serological testing with an indirect immunofluorescence assay is the most commonly used laboratory method to diagnose Q fever endocarditis.[5] *C. burnetii* phase I IgG was found to be positive with a 1:32768 titer in our patient, which led to the diagnosis. Diagnosis of Q fever endocarditis is frequently delayed as a result of the unfamiliarity

of doctors with this type of endocarditis, subdued clinical presentation, absence of vegetation on echocardiographic investigation, and blood culture negativity.[5–7] In the other 2 cases treated at our institution, the diagnosis was established for the patients after 5 years and 2 years, respectively. Diagnostic delay is associated with mortality in Q fever endocarditis, and these late-diagnosed patients died due to endocarditis. This patient is our third case, and he was admitted to our hospital with a 1-month history of constitutional symptoms. He was diagnosed early in the course of the disease, and this early diagnosis greatly contributed to his survival.

Response to treatment of Q fever endocarditis should be monitored serologically, and the *C. burnetii* phase I IgG level should be measured every 3 months. Treatment can be terminated if the titer of IgG antibodies against phase I antigens decreases by at least 4-fold, or decreases to a titer level of less than 1:800. The duration of treatment is 24 months for those with prosthetic valves. We monitored our patient's response to therapy with phase I IgG level and observed a 4-fold decrease at the 20th month of treatment. The patient was scheduled to continue treatment for an additional 4 months.

Apart from the causative agent, this case is important because of the clinical presentation. Endocarditis is thought to occur in about 1% of all patients following acute infection with Q fever,[8] and is considered to be a late complication of Q fever in patients with preexisting valvular heart disease. Our patient was admitted to the hospital for fever and constitutional symptoms present for only 1 month, and he developed NYHA class IV HF and a large vegetation. The clinical course was more consistent with acute endocarditis. Vegetation is absent in nearly 50% of Q fever endocarditis cases, or may be missed, because they are usually located subendothelially and are often smaller in comparison with those caused by other organisms.[9] The detection of prominent vegetation on an echocardiogram in a patient with Q fever seen in our case differs from studies in the literature. It may have been an instance of antiphospholipid antibody syndrome with valvular vegetation in acute Q fever, which has been described recently,[10] but we were unable to test for anticardiolipin antibodies early on, and as a result, unfortunately, we cannot prove this. Another reason for the rapid clinical course in our patient could be the prior treatment with a steroid, which could have contributed to the clinical deterioration. The effect of systemic steroids on the outcome of bacterial IE is not well known. However, in a case report submitted by Ahmad et al.,[11] 2 patients diagnosed with definite IE had first received steroids due to a probable rheumatological disorder, and 1 died due to acute respiratory distress syndrome.

Symptoms of dyspnea are also important to recognize, because HF is the most common complication of IE, has the greatest impact on prognosis, is the most frequent indication for surgical intervention, and is the most important predictor of a poor outcome with surgical therapy for IE.[12] Our patient had persistent dyspnea, pulmonary crackles, and pretibial edema, despite intensive diuretic therapy.

The data from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study[13] showed that patients with acute decompensated HF had much higher NT- proBNP values compared with patients without HF, and that a greater NT-proBNP level correlated well with increasing severity of HF. Our patient's high NT-proBNP level was consistent with the rapid and severe onset of HF.

When evaluating a patient with new HF or decompensated HF, identification and correction of a precipitating cause is crucial. In our case, severe anemia and systemic inflammation due to Q fever substantially contributed to the severe presentation and caused a high-output state. NYHA class IV HF was inevitable with the accompanying echocardiographic features of severe aortic regurgitation, left ventricular hypertrophy, grade II diastolic dysfunction, and severe systolic pulmonary hypertension. Surgical replacement of an aortic valve was performed due to IE and refractory HF.

Conclusion

C. burnetii should be always taken into consideration in cases of BCNE, and a *Coxiella* Phase I IgG determination may easily lead to a final diagnosis. Although Q fever endocarditis generally has a subacute or chronic clinical course with small or no vegetation, an acute course with large vegetation and advanced HF may also be seen. As the effect of systemic steroids on the outcome of bacterial IE can be devastating, these drugs should be avoided as much as possible in a case of BCNE.

**Supplementary video file associated with this article can be found in the online version of the journal.*

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Keywords: Acute Q fever endocarditis; *Coxiella burnetii*; echocardiogram; heart failure; infective endocarditis; Q fever; valve replacement; vegetation.

Anahtar sözcükler: Akut Q ateşi endokarditi; *Coxiella burnetii*, ekokardiyogram; kalp yetersizliği; enfektif endokardit, Q ateşi; kapak replasmanı; vejetasyon.