

First Case of Q Fever Endocarditis in Croatia and a Short Review

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ABSTRACT

We present a 70-year-old man from Dalmatia, Croatia, with a history of prolonged high fever diagnosed as Q fever endocarditis. As far as we know, this is the first case of chronic Q fever in Croatia. The treatment was started as for culture-negative endocarditis, but was without clinical response. After significantly high anti-phase I IgG plus IgA antibodies titers to *Coxiella burnetii* were shown, the initial treatment with doxycycline was changed and ciprofloxacin was started with good clinical response.

Key words: Q fever, endocarditis, Croatia

Introduction

Q fever has been a well-known and mandatory notable disease in Croatia from 1954¹. It usually occurs sporadically as an occupational disease in areas predominantly rich with sheep and goats. The first greater outbreaks in Dalmatia have been reported quite recently². Typically, in Croatia the disease manifests as atypical pneumonia. Until the present no Q fever endocarditis has been described.

Case Report

A 70-year-old sheep farmer from North Dalmatia was admitted to Zadar General Hospital due to prolonged two-week high intermittent fever and minimal paroxysmal coughing, not previously treated with antibiotics. His past medical history was significant only for paroxysmal atrial fibrillation and mitral valve prolapse evidenced two years earlier. On examination, he had an ejection holostolic murmur that radiated to the axillar region, and 3-centimeter splenomegaly. Routine blood tests revealed ESR 85 mm/h, CRP 37 mg/L, Hemoglobin 12.6 g/dL; white-cell count $10.5 \times 10^9/L$ with 76% neutrophils, 10% lymphocytes, 7% monocytes, 4% band forms; platelets $253,000/mm^3$; aspartate aminotransferase 29 U/L, alanine aminotransferase 24 U/L; blood glucose 6.4

mmol/L urea nitrogen 4.2 mmol/L, creatinine 73 mmol/L; total protein 82.0 g/L (gamma globulins 34.2%). Due to the fact that splenomegaly suggested the possibility of malignancy, chest X-ray, abdominal ultrasound, urologic examination, bone marrow aspiration, gastroscopy and tumor markers were performed, and all were normal. Transthoracic (TTE) and transoesophageal echocardiogram (TEE) revealed mitral valve prolapse with moderate mitral regurgitation; but without visible vegetations.

Serial blood cultures (anaerobic and aerobic), as well as the bone marrow culture for the isolation of *Brucella* spp., were negative. The patient was initially treated with ampicilin and gentamicin+ceftriaxon with no clinical response. After the pair serological testing for *Coxiella burnetii* antibodies proved positive, (ELISA tests for *Bartonella* spp., *Legionella* spp. and *Chlamydia* spp. were negative as well as the serum agglutination and complement fixation tests for *Brucella* spp.), a combination of doxycycline and ciprofloxacin was started. Several days after the patient became afebrile; he was discharged and sent home to be followed-up clinically and serologically as an outpatient (Table 1).

Three months later, ciprofloxacin was replaced by hydroxychloroquine with further good clinical result and no adverse effects. Therefore, the patient was told to con-

TABLE 1
SEROLOGICAL FINDINGS IN A PATIENT WITH Q FEVER
ENDOCARDITIS

Date (mo/day/yr)	Anti-phase I*		Anti-phase II*	
	IgG	IgA	IgG	IgM
05/16/08	Borderline 1.1 index ¹	Positive 1.5 index ²	Positive 146 U/mL ⁴	Positive 1.9 index ¹
06/05/08	Borderline 1.0 index	Borderline 1.1 index	Positive 89 U/mL	Positive 2.4 index
07/23/08	Borderline 1.0 index	Negative ³	Positive 129 U/mL	Positive 2.2 index
09/25/08	Positive 1.2 index	Negative	Positive 113 U/mL	Positive 1.6 index
12/16/08	Negative	Negative	Positive 82 U/mL	Positive 1.2 index

*ELISA – enzyme-linked immunosorbent assay

¹borderline index 0.9–1.1; ²positive index >1.1; ³negative index

tinue with the treatment for another 12 months, 18 months in total. Repeated transthoracic echocardiogram showed no new changes in this period. Also, routine blood tests became normal and splenomegaly resolved.

Discussion

In Croatia, Q fever has been known almost exclusively through the clinical feature of atypical pneumonia^{3–5}. Since Dalmatia is an old endemic Q fever area, for years all culture-negative endocarditis have been searched for *Coxiella burnetii* antibodies but without further systematical follow-up of the patients after the acute Q fever phase. To our knowledge, this case represents the first documented Q fever endocarditis in Croatia.

In some countries it is estimated that Q fever endocarditis represents 8.7–11% of all reported Q fever cases; in France it represents 5% of endocarditis cases with the incidence of 1 case per million inhabitants per year^{6,7}. Also, it is estimated that the risk of transformation from acute Q fever to endocarditis is about 40% in patients with valvulopathy⁸. In our patient acute Q-fever manifested as a flu-like illness transformed into chronic disease very soon, after a few weeks. It is possible that relatively quick disappearance of phase I antibodies to *C. burnetii* is the result of prompt and appropriate treatment given after positive serology was obtained. In many cases the development of endocarditis after acute Q fever may take months to years^{9,10}.

Endocarditis with a negative blood culture accounts for up to 48% of infective endocarditis cases^{11–14}. About half of the cases is due to previous antibiotic treatment^{13,15} while the main other causes are fastidious growing bacteria. In the case of our patient, who had not been previously treated with antibiotics, blood and bone marrow cultures were negative as were the other serological tests except that for *C. burnetii*. Among the fastidious microorganisms, the most common identified are

Coxiella burnetii and *Bartonella* spp., rarely *Brucella* spp., *Abiotrophia* spp., HACEK group, *Listeria monocytogenes* and very rarely *Legionella* spp., *Mycoplasma* spp., *Aspergillus* spp. etc.^{6,7,16}. Routine serological testing for these bacteria depends on the local epidemiological feature and local standards. In this regard, broad-range PCR and sequencing could be helpful for identification of bacterial DNA^{17,18}.

The diagnosis of Q fever endocarditis by echocardiography is problematic because the vegetations are absent or small. In this regard, TEE appears to be of greater usefulness than TTE because of better sensitivity and possibility for detecting mechanical complications^{19,20}. The usefulness of echocardiography has led to its inclusion in the so-called »Duke-criteria« for the diagnosis of endocarditis. This criterion classifies the diagnosis of infective endocarditis and then echocardiographic findings²¹. Moreover, some reports suggested that modification of current diagnostic criteria was required and that would include serology and molecular diagnostic of fastidious bacteria^{22–24}. It is estimated that the overall sensitivity of the Duke criteria is about 80%. By using serologic methods for identification of fastidious microorganisms about 9% of IE patients with negative blood culture could be reclassified from »definite IE« category to »possible IE« and about 7% from »rejected IE« to »possible IE«¹⁶. The molecular PCR method has led to an increase in sensitivity of the Duke criteria, but, at the same time, to a decrease in specificity; moreover, at present there is no standardization of this methodology.

In the case of *Coxiella burnetii* endocarditis, the most commonly used serologic methods are indirect immunofluorescence assay (IFA) and enzyme-linked immunosorbent assay (ELISA)^{25,26}. IFA test is needed as confirmatory test only in the case of negative EIA (enzyme immunoassay) test²⁶. Antibodies to phase I and phase II can be determined in the IgG, IgM and IgA classes. Q fever endocarditis is characterized by a very high titer of anti-phase I IgG antibodies.

The treatment of Q fever endocarditis evolved through the years, and, at present, the optimal regimen include doxycycline in combination with fluoroquinolone or with hydroxychloroquine^{27–29}. The first combination should last at least 3 years, the second at least 18 months. Q fever is considered cured when the anti-phase IgG titers are less than 800³⁰.

Conclusion

Q fever endocarditis occurs principally in patients with valvular damage and is diagnosed according to the modified Duke criteria^{7,8}. Some authors proposed that every patient with acute Q fever and valvulopathy should be followed-up serologically for at least 2 years, if necessary by PCR and also by TTE^{8,31,32}. This approach could be of great help because in patients with valvular damage there exists the significant risk of endocarditis, and specially because endocarditis could happen many years after acute infection^{10,33}. Moreover, some authors suggest

that all the patients with acute Q fever, irrespective whether the underlying factors exist or not, should be systematically tested for anti-phase I and II *Coxiella burnetii* antibodies at 3 to 6 months intervals after the

disease onset³⁴. Our case report supports these recommendations which can be very useful in Q fever endemic areas like Dalmatia in Croatia.

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PRVI SLUČAJ KRONIČNE Q GROZNICE S ENDOKARDITISOM I KRATKI PREGLED

SAŽETAK

Prikazujemo slučaj 70-godišnjeg bolesnika iz Dalmacije kod kojega je nakon dugotrajne vrućice dokazan endokarditis kao kronični oblik Q groznice. Prema našim saznanjima radi se o prvom takvom slučaju u Hrvatskoj. Liječenje je započeto kao u kultura-negativnih endokarditisa bez kliničkog odgovora. Nakon dobivanja nalaza visokih titrova IgG i IgA protutijela na fazu I *Coxiella burnetii* terapija je promjenjena u doksiciklin i ciprofloksacin s dobrim kliničkim odgovorom.