Original Article

Defining the clinical characteristics of Q fever endocarditis: A case-control study in China

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Abstract

Introduction: Q fever is a worldwide zoonosis caused by *Coxiella burnetii*. Atypical presentations of Q fever can cause diagnostic difficulty or be misdiagnosed. Here we compared the clinical and diagnostic features of Q fever endocarditis and endocarditis caused by other bacteria to identify features of Q fever endocarditis that might facilitate early diagnosis.

Methodology: This was a retrospective case-control study of eight cases of Q fever endocarditis diagnosed between 2000 and 2018 at Peking Union Medical College Hospital in China and 24 age- and gender-matched patients diagnosed with bacterial endocarditis over the same period. Clinical and laboratory data were collected and compared between groups.

Results: The median time interval between symptoms and diagnosis was significantly longer in the case group than the control group (8.0 months (IQR 7.0-16.0) vs. 4.0 months (IQR 1.0-7.0); $p = 0.002$). Patients in case group had significantly lower white blood cell counts ($5.8 \pm 2.4 \times 10^9$/L vs. $10.0 \pm 3.4 \times 10^9$/L; $p = 0.003$), percentage of neutrophil ($62.4 \pm 14.7\%$ vs. $79.1 \pm 9.2\%$; $p = 0.014$), high-sensitivity C-creative protein levels (21.1 mg/L (IQR 18.5-32.8) vs. 45.3 mg/L (IQR 32.9-54.3); $p = 0.038$), and platelet counts (133 ± 73 vs. 229 ± 65; $p = 0.001$) but higher levels of rheumatoid factor (104.3 U/L (IQR 99.0-132.8) vs. 10.2 U/L (IQR 6.9-32.5); $p = 0.011$) than controls. Elevated creatinine (50.0% vs. 12.5%; $p = 0.047$) and liver enzymes (50.0% vs. 0%; $p = 0.002$) were more common in cases than controls. Q fever endocarditis was less frequently diagnosed than controls before cardiac surgery (62.5% vs. 100%; $p = 0.011$), with negative blood cultures in all cases.

Conclusions: The diagnosis of Q fever endocarditis can easily be delayed compared to other causes of infectious endocarditis. Patients with chronic fever and new valve dysfunction require careful assessment, especially when presenting with negative blood cultures and high rheumatoid factor levels. Clinical and laboratory evaluation of these patients should include routine serological testing for *C. burnetii.*

Key words: *Coxiella burnetii*; infectious endocarditis; Q fever; diagnosis.

Introduction

First described in 1937 by Derrick in Queensland, Australia [1], Q fever is a widely distributed zoonotic infection caused by *Coxiella burnetii*, an obligate, intracellular, Gram-negative bacterium [2,3]. *C. burnetii* can survive in the environment for very long periods and is highly infectious. Humans are usually infected through aerosols but may occasionally be infected through the digestive tract, percutaneous exposure, transfusion, or sexual intercourse [4].

Clinical manifestations of Q fever are variable, from asymptomatic seroconversion to severe disease. The disease is commonly divided into acute and chronic infections [5,6]. After acute infection, 40 to 60% of patients remain asymptomatic, while others develop symptoms ranging from a self-limiting flu-like syndrome to severe manifestations including pneumonia and hepatitis. Following acute infection, 1 to 5% of patients progress to chronic infection [7]. Chronic Q fever presents mainly as endocarditis, which is the most severe and potentially fatal form of chronic Q fever [3,8].

There are few reports of Q fever endocarditis in China. The incidence of Q fever infection in China may be low, but it is also possible that some cases are misdiagnosed due to a lack of awareness about the infection. A lack of clinical awareness can also delay the diagnosis or lead to under-diagnosis. Therefore, the objective of this case-control study was to compare the clinical manifestations of Q fever endocarditis with other forms of bacterial endocarditis to identify

diagnostic clues of Q fever endocarditis that might facilitate early and accurate diagnosis.

Methodology
Study design and participants

This was a retrospective, case-control, observational study of eight patients diagnosed with Q fever endocarditis between January 1, 2008, and December 31, 2018, at Peking Union Medical College Hospital, a university-affiliated tertiary hospital in China. Q fever endocarditis was diagnosed using modified Duke infective endocarditis criteria [3,9,10]. which include *C. burnetii* anti-phase I IgG antibody titer of ≥ 1:800 or a positive blood culture as a major criterion, transoesophageal echocardiographic (TEE), and/or histopathological findings of a valve consistent with endocarditis as a major criterion. We also excluded Brucellosis and other blood culture-negative endocarditis (endocarditis related to fastidious microorganisms and intracellular bacteria). To explore the clinical characteristics of Q fever endocarditis, each Q fever endocarditis patient was matched with three control patients with infective endocarditis caused by common bacteria identified in the same hospital over the same time. Matching criteria were gender, age (± 3 years), and treatment at the same time as the Q fever endocarditis diagnosis case.

Demographic and clinical data

Detailed clinical and laboratory data were retrieved from the patient's medical records. Patient demographics, risk factors for infective endocarditis, past medical history, symptoms, and examination findings at presentation data were collected. Clinical features not documented in the medical records were assumed to be absent. The ethics committee of Peking Union Medical College Hospital approved the study protocol, and all data collected were de-identified.

Statistical analysis

Data were processed and analyzed using SPSS (v20, IBM Statistics, Armonk, NY). Quantitative variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR). Qualitative variables are expressed as numbers and percentages. Continuous variables with normal and skewed distributions were compared using Student's *t*-test and the Wilcoxon rank-sum test, respectively. Categorical variables were compared using the χ^2 test. A P value < 0.05 was considered statistically significant.

Ethical approval

The ethics committee of Peking Union Medical College Hospital approved the study (S-K 1343), and all data collected were de-identified.

Results

Thirty-two patients with infective endocarditis were enrolled in the study, eight Q fever endocarditis cases (detailed in Table 1) and 24 controls. The case and control groups were comparable with respect to mean

Table 1. Clinical characteristics of patients with Q fever endocarditis.

Patient	Year of diagnosis	Age[a]/ Gender	Symptoms and signs	Complications	Duration of symptoms prior to diagnosis	Risk factors
1	2008	41/Male	Fever, yellow skin and sclera, fatigue, hepatomegaly	Severe liver dysfunction	11 months	Bicuspid aortic valve, close contact with cattle and sheep, splenectomy
2	2009	61/Male	Fever, rashes, fatigue, weight loss, night sweats, splenomegaly	Elevated liver enzymes	4 months	Aortic valve thickening and calcification, tricuspid valve prolapse
3	2010	21/Male	Fever, cough, chest pain, splenomegaly	Elevated liver enzymes, myocarditis, pneumonia, respiratory failure	4 months	None
4	2012	54/Male	Fever, knee pain, chest tightness, shortness of breath	Cerebral embolism	24 months	Congenital aortic valve dysplasia, bicuspid aortic valve
5	2014	58/Male	Fever, fatigue, shortness of breath		48 months	None
6	2015	55/Male	Fever, poor appetite, weight loss, cough, hepatomegaly and splenomegaly	Pneumonia	6 months	Rheumatic heart disease, veterinarian, close contact with cattle, sheep and horses
7	2017	44/Male	Fever, fatigue, weight loss	Elevated liver enzymes, cerebral embolism	4 months	Bicuspid aortic valve
8	2017	65/Female	Fever, fatigue, weight loss, splenomegaly	Severe anemia, chronic kidney disease	8 months	Mechanical prosthetic valve

[a]Age at diagnosis.

Table 2. Comparison of demographic and clinical data of cases and matched controls.

Variables	Q fever group (n = 8)	Control group (n = 24)	*p* value
Age, years	49.9 ± 14.2	49.7 ± 14.1	0.971
Gender, male %	7 (87.5%)	21 (87.5%)	1.000
Time interval between symptoms and diagnosis, months	8.0 (7.0, 16.0)	4.0 (1.0, 7.0)	**0.002**
With risk factors of IE, %	75.0% (6/8)	54.2% (13/24)	0.420
Symptom at presentation			
Fever, %	100% (8/8)	95.8% (23/24)	1.000
Arterial embolism, %	37.5% (3/8)	29.2% (7/24)	0.681
Pneumonia, %	25.0% (2/8)	12.5% (3/24)	0.578
Valvular vegetation, %	75.0% (6/8)	100% (24/24)	0.056
Vegetation detected by TEE, %	33.3% (2/6)	4.2% (1/24)	0.094
Diagnosed before cardiac surgery, %	62.5% (5/8)	100% (24/24)	**0.011**
Cardiac surgery, %	50.0% (4/8)	91.7% (22/24)	**0.023**

Data are no. (%) of patients and no. of patients with the characteristic/total no. of patients for whom data were available. IE: infective endocarditis; TEE: transesophageal echocardiography.

age (49.9 ± 14.2 and 49.7 ± 14.1 years; *p* = 0.971) and male gender (87.5% and 87.5%; *p* = 1.00) (Table 2).

Clinical features

The demographic and clinical comparisons of cases and matched controls are presented in Table 2. The median time interval between symptoms and diagnosis was significantly longer in the case group than in the control group (8.0 months (IQR 7.0-16.0 months) vs. 4.0 months (IQR 1.0-7.0 months); *p* = 0.002). Six patients (75%) in the case group and 11 patients (54.2%) in the control group presented with previous and known cardiovascular abnormalities (*p* = 0.299). There was no significant difference in the occurrence of embolism between the case and control groups (three patients (37.5%) vs. seven patients (29.2%); *p* = 0.681). The frequency of pneumonia between the two groups was not significantly different (two patients (25.0%) vs. three patients (12.5%); *p* = 0.578).

Laboratory findings

The laboratory findings in cases and controls are presented in Table 3. The case group had significantly lower white blood cell (WBC) counts (5.8 ± 2.4 × 10^9/L vs. 10.0 ± 3.4 × 10^9/L; *p* = 0.003), high-sensitivity C creative protein levels (hsCRP) (21.1 mg/L (IQR 18.5-32.8) vs. 45.3 mg/L (IQR 32.9-54.3); *p* = 0.038), and platelet counts (133 ± 73 vs. 229 ± 65; *p* = 0.001). The case group had higher percentage of lymphocyte (30.8 ± 12.9% vs. 13.5 ± 6.4%; *p* = 0.006) and lower percentage of neutrophil (62.4 ± 14.7% vs. 79.1 ± 9.2%; *p* = 0.014). The case group had higher rheumatoid factor (RF) antibody levels (104.3 U/L (IQR 99.0-132.8) vs. 10.2 mg/L (IQR 6.9-32.5); *p* = 0.011) and a

Table 3. Comparison of laboratory data for cases and matched controls.

	Q fever group (n = 8)	Control group (n = 24)	*p*-value
Hemoglobin, g/L	109 ± 28	109 ± 19	0.996
Platelet, × 10^9/L	134 ± 73	226 ± 64	**0.002**
White blood cell, ×10^9/L	5.8 ± 2.4	9.8 ± 3.3	**0.003**
Neutrophil, %	62.4 ± 14.7	79.1 ± 9.2	**0.014**
Lymphocyte, %	30.8 ± 12.9	13.5 ± 6.4	**0.006**
ESR, mm/h	57 ± 45	58 ± 31	0.905
hsCRP, mg/L	21.1 (18.5, 32.8)	45.3 (32.9, 54.3)	**0.038**
Albumin, g/L	33.5 ± 3.5	33.8 ± 4.8	0.886
Total bilirubin, μmol/L	9.8 (8.9, 11.8)	10.8 (8.8, 13.2)	0.741
Creatinine, μmol/L	112 (69, 167)	72 (67, 88)	0.199
Serum ferritin, ng/mL	324 (160, 337)	371 (272, 739)	0.171
Rheumatoid Factor, IU/L	104.3 (99.0, 132.8)	10.2 (6.9, 32.5)	**0.011**
Immunoglobulin G, g/L	19.2 ± 5.9	16.2 ± 4.5	0.215
Cardiac troponin I,	0.035 (0.007, 0.614)	0.057 (0.014, 0.116)	0.727
NT-proBNP,	990 (935, 8694)	1683 (551, 2679)	0.817
Autoantibody positive, %	42.9% (3/7)	53.8% (7/13)	1.000
Complement level decrease, %	0 (0/7)	38.5 (5/13)	0.114
Urine red blood cell positive, %	50.0% (4/8)	50.0% (12/24)	1.000
Urine protein positive, %	37.5% (3/8)	12.5% (3/24)	0.148
Increased ALT level, %	50.0% (4/8)	0 (0/24)	**0.002**
Increased creatinine level, %	50.0 (4/8)	12.5% (3/24)	**0.047**
Blood culture positive, %	0 (0/8)	95.8% (23/24)	**< 0.001**

Data are no. (%) of patients and no. of patients with the characteristic/total no. of patients for whom data were available. ESR: erythrocyte sedimentation rate; hsCRP: high-sensitivity C-reactive protein; ALT: alanine aminotransferase; NP-proBNP: N-terminal pro b-type natriuretic peptide.

higher frequency of elevated creatinine (four patients (50.0%) vs. three patients (12.5%); *p* = 0.047). In the case group, four patients had elevated liver enzymes during the course of the disease, but none in the control group (*p* = 0.002) (Table 3).

There were no differences in cardiac troponin I or N-terminal pro b-type natriuretic peptide (NP-proBNP) levels between the two groups. There were also no differences in hemoglobin, erythrocyte sedimentation rate (ESR), albumin, total bilirubin, serum creatinine, serum ferritin, serum immunoglobulin G (IgG), or the frequency of urine red blood cell (RBC) or protein positivity between groups (Table 3).

Of the seven Q fever endocarditis patients who had autoantibody tested, three patients (42.9%) had positive autoantibodies: two with antinuclear antibodies (ANA), two with anticardiolipin antibodies (Acl), one with antineutrophil cytoplasmic antibodies (ANCA), and two Coombs test positive. Of 13 patients with autoantibody tested in the control group, seven patients (53.8%) had positive antibodies: three with ANA, four with ANCA, one with double-stranded DNA, and one with anti-SSA. The frequency of antibody positivity was not significantly different between the two groups (*p* = 1.000). In seven Q fever endocarditis patients with available complement levels, all were in the normal range, while complement levels were decreased in five patients (38.5%) of 13 tested control patients (*p* = 0.114) (Table 3).

The blood culture results of the case group were all negative. Of the 24 control cases, blood cultures revealed *Streptococcus* spp. in 19 patients, which is the most frequently isolated microorganism in infective endocarditis. Four patients were infected with methicillin-sensitive *Staphylococcus aureus*, *Enterococcus faecalis*, *Brucella* spp., and *Nocardia* spp., respectively. In one patient, no microorganisms were identified.

Imaging findings

Transesophageal/transthoracic echocardiography (TEE/TTE) was performed on all case and control patients. In the case group, valvular vegetations were identified in six patients (6/8, 75.0%); four on the aortic valve, one on the mitral valve, and one on both the aortic and tricuspid valves. Valvular vegetations were only identified by TEE in two patients (patient 6 and patient 7) and could not be detected by TTE (Table 4). In the control group, all patients had vegetations (24/24, 100%): ten on the aortic valve, seven on the mitral valve, one on the pulmonary valve, four on both the mitral and aortic valves, one on both the aortic and pulmonary valves, and one on both the mitral and tricuspid valves. Valvular vegetations were detected by TTE in 23 patients. There was a significant difference in the frequency of receiving TEE (4/8 (50.0%) vs. 3/24 (12.5%); p = 0.047) between the two groups.

Diagnosis, treatment, and prognosis

Significantly fewer Q fever endocarditis than control cases were diagnosed prior to cardiac surgery (five patients (62.5%) vs. 24 patients (100%); *p* = 0.011). In the case group, one patient (patient 7) was diagnosed after surgery, while two patients (patients 4 and 5) were not even diagnosed after valve replacement; these patients recurred 17 and 8 months

Table 4. TEE/TTE and serology results of patients with Q fever endocarditis.

Patient	Results of TEE/TTE				Diagnosis		Treatment	Outcome
	Valve involved	Vegetation	Abscess	Valvular function	IgG Phase I	IgG Phase II		
1	Aortic	+	+	Moderate aortic stenosis with mild insufficiency, moderate tricuspid insufficiency, moderate pulmonary hypertension	1:320	1:320	Minocycline 0.1 bid	Lost to follow-up
2				Mild aortic insufficiency, moderate tricuspid insufficiency	≥ 1:5120	1:3200	Doxycycline 0.1 bid,	Treated for 12 months, stable
3	Mitral	+	-		Positive	Positive	Doxycycline 0.1 bid	Treated for 30 months, stable
4	Aortic, tricuspid	+	-	Postoperative aortic valve replacement, mild-moderate perivalvular aortic leak, mild mitral insufficiency	1:3200	1:800	Minocycline 0.1 bid, HCQ 0.2 tid	Mechanical aortic valve replacement after diagnosis 12 months later for heart failure
5	Aortic	+	+	Postoperative aortic and mitral replacements, perivalvular aortic leak	1:6400		Minocycline 0.1 bid, HCQ 0.2 tid	Treated for 30 months, stable
6	Aortic	+	-	Severe aortic stenosis with mild insufficiency, mild mitral stenosis with mild insufficiency	> 1:1600	> 1:1600	Doxycycline 0.1 bid, HCQ 0.2 tid	Treated for 18 months, stable
7	Aortic	-	+	Moderate-severe aortic insufficiency	1:3200	1:400	Doxycycline 0.1 bid, HCQ 0.2 tid	Treated for 24 months, stable
8				Postoperative aortic valve replacement, mild mitral insufficiency	1:3200	1:3200	Doxycycline 0.1 bid, HCQ 0.2 tid	Died of heart failure

IgG: immunoglobulin G; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography; HCQ: hydroxychloroquine.

later and were then diagnosed with Q fever endocarditis. In the control group, all patients were diagnosed before the operation, and 22 patients underwent surgical treatment.

All Q fever endocarditis patients were treated with oral antibiotics. Three patients received an antibiotic (doxycycline or minocycline). With a further understanding of the disease, the latter 5 patients were treated with doxycycline or minocycline in combination with hydroxychloroquine (Table 4).

One patient was lost to follow-up. Of the other seven patients, the median follow-up was 64 months (range 9-120 months) (Table 4). Another patient stopped treatment after three months due to severe digestive tract reactions and died seven months later of refractory heart failure. Six patients were deemed clinically cured at follow-up, one of whom had received a mechanical aortic valve replacement 12 months after diagnosis for heart failure. No patient had detectable antibody titers after treatment.

Discussion

Q fever endocarditis is a relatively rare disease, accounting for 5% of blood culture-negative endocarditis cases [11,12]. This case-control study advances our knowledge of the specific clinical features of Q fever endocarditis. The inflammatory response in Q fever endocarditis patients was more moderate than that in bacterial infective endocarditis patients; RF levels in Q fever endocarditis were higher; Q fever endocarditis patients were more likely to have biochemical indicators of other organ dysfunction.

The WBC, the percentage of neutrophil, platelet, and hsCRP levels were lower in the case group than in the control group. Compared to bacterial endocarditis, the inflammatory response in Q fever endocarditis patients appears to be more moderate. This may be due to the characteristics of *C. burnetii,* which is a strict intracellular bacterium that lives in host phagocytes. The course of Q fever endocarditis is mostly chronic [10,11].

Q fever endocarditis patients were more likely to have elevated creatinine and liver enzymes during the course of the disease. Q fever is characterized by its clinical heterogeneity, as it can be associated with the vast majority of infectious syndromes and can be both acute and chronic. Endocarditis is the major clinical presentation of chronic Q fever, although chronic Q fever infection can also present with hepatitis, pneumonia, meningitis, pericarditis, and myocarditis [10,11]. Therefore, our findings of abnormal laboratory parameters in other organs are consistent with this heterogeneity.

The clinical manifestations of Q fever endocarditis are known to be diverse and atypical, often delaying the diagnosis [13]. We found that the time interval between onset and diagnosis in the case group was four months longer than that in the control group. The laboratory diagnosis of Q fever endocarditis can be challenging because *C. burnetii* has growth requirements that rule out routine culture. As observed in our cases, the symptoms of Q fever endocarditis were non-specific and the blood culture results were negative in all patients.

Two patients with Q fever endocarditis did not have detectable vegetations at echocardiography. Cardiac valve vegetations are usually absent or small in patients with Q fever endocarditis, so they are not always detected by TTE [14,15]. Million *et al.* found that two-thirds of Q fever endocarditis cases had no detectable vegetations, and sometimes only systematic examination of the valves at the time of valve replacement permitted the diagnosis [3]. The vegetations were only detected by TEE in two of our Q fever endocarditis patients, demonstrating that TEE is more sensitive to the detection of valve vegetations. For patients with suspected infectious endocarditis, TEE is advisable if no vegetations are found by TTE.

A lack of clinical awareness or testing methods may also delay the diagnosis or lead to under-diagnosis [11]. The diagnostic delay has a significant effect on the patient's prognosis, with mortality approaching 100% and the need for surgery as high as 60% if untreated [7]. Although *C. burnetii* diagnostics are included in the modified Duke criteria for the diagnosis of infective endocarditis, systematic serological testing for *C. burnetii* is not common in practice. In our study, the diagnosis of Q fever endocarditis was unexpected in three of eight patients and only diagnosed after cardiac surgery or even after recurrence in two of these patients. In the control group, vegetation were detected and the diagnosis was made before surgery in all cases. Our results suggest that clinicians must have a high index of suspicion for Q fever when investigating chronic fever in the presence of new valve dysfunction, elevated RF, a normal WBC, elevated liver enzyme and creatinine levels, and negative blood cultures. All patients with culture-negative endocarditis should be tested for Q fever, as must endocarditis patients in whom the disease progresses when receiving empirical antimicrobial agents.

Endocarditis is often associated with systemic immune manifestations. Chronic Q fever can mimic

vasculitis and may be associated with cryoglobulinemia and Crohn's disease [5]. We found that RF levels were higher in Q fever endocarditis patients than in non-Q fever controls. Three of five patients had elevated 24-hour urine protein levels. Autoantibody positivity is not uncommon in Q fever; indeed, anti-phospholipid (aPL) antibodies are a common immunological event in the setting of Q fever. Their activity is mostly β2GP1-independent (infectious-type aPL) and rarely associated with thrombotic events. A variety of other autoantibodies have been described in Q fever, including ANA and ANCA [5]. *C. burnetii* infection presents with atypical features suggesting the inflammatory systemic disease is therefore easily misdiagnosed. Q fever endocarditis should be differentiated from non-infective endocarditis related to systemic lupus erythematosus and Behcet's disease since both can cause blood culture-negative endocarditis [12].

There were several limitations to this study. First, this was a retrospective study conducted in a single center. It is possible that some important epidemiological and clinical details were not recorded or missed. Second, the sample number was small, so the results might not be representative and may contain bias. Q fever endocarditis is a rare condition, and our institution is a specialist center for complicated and severe cases while less severe cases may have been managed elsewhere, again introducing bias.

Conclusions

In conclusion, here we describe in detail the clinical characteristics of Chinese patients with Q fever infective endocarditis. The diagnosis was unexpected in three of eight patients and was delayed until after elective valve surgery or even recurrence. Events such as these are probably underdiagnosed due to the protean manifestations of Q fever endocarditis. Our results suggest that routine serological testing for *C. burnetii* should be considered in patients with chronic fever and new valve dysfunction, especially when patients present with negative blood cultures and high RF levels. Further prospective studies in larger cohorts of patients will further increase our understanding of this condition.

Authors' Contributions
XZ and YJ designed the study; XZ, HF, and XH collected data and analyzed the results; XZ and YJ drafted the manuscript; XH and YJ provided supervision or mentorship; all authors revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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