

A Case Report of Infective Endocarditis with Failure of the Empirical Treatment—Q Fever Endocarditis Diagnosed by Metagenomic Next-Generation Sequencing

Guo-Shuai Lin*, Mao-Mao Zhao*, Xiao-Qing Li, Hong-Xia Yu

Department of Infectious Disease, Yantai Yuhuangding Hospital, Yantai, Shandong, 264000, People's Republic of China

*The authors contributed equally to this work

Correspondence: Hong-Xia Yu, Department of Infectious Disease, Yantai Yuhuangding Hospital, Yantai, Shandong, 264000, People's Republic of China, Tel +86 15053573266, Email yuhongxiag6d@163.com

Background: Infective endocarditis (IE) can be caused by a variety of pathogens. Endocarditis due to the *Coxiella burnetii* (*C. burnetii*) infection is common in patients with negative blood culture results and usually occurs in patients with previous valvular heart disease, impaired immune function, and during pregnancy. The diagnosis is difficult based on the conventional diagnostic method, and serious adverse outcomes may occur in the case of delayed diagnosis.

Case Report: In the present study, a case of a 43-year-old male patient with previous valvular heart disease was reported. The patient was admitted with a diagnosis of IE, but the etiology was unclear. Accurate diagnosis and treatment were achieved by combining metagenomic next-generation sequencing (mNGS) with Q fever serological antibody assay.

Conclusion: Metagenomic next-generation sequencing has been increasingly applied in clinical practice in recent years to detect the DNA or RNA in samples, and this could play a decisive role in the etiological diagnosis of some infectious diseases.

Keywords: Q fever, endocarditis, diagnosis, metagenomic next-generation sequencing

Introduction

Q fever is a naturally occurring epidemic disease caused by the *Coxiella burnetii* (*C. burnetii*) infection. The hosts of *C. burnetii* include mammals, birds, arthropods, etc. It is found in most countries around the world and is mainly transmitted through aerosols.¹ The clinical manifestations of patients with Q fever who usually have contact with animals are diverse and Q fever can be divided into acute and chronic infections, with chronic infections being more common. Q fever endocarditis is the most common manifestation of chronic infection and usually occurs in patients with previous valvular heart disease, impaired immune function, and during pregnancy.² However, Q fever endocarditis is difficult to diagnose clinically and may lead to very serious or even life-threatening outcomes if not diagnosed promptly. In the present study, a case of Q fever endocarditis that occurred based on valvular heart disease was reported. Accurate diagnosis and treatment were achieved by metagenomic next-generation sequencing (mNGS) combined with detection of the Q fever serological antibodies.

Case Report

A 43-year-old male patient who had suffered from chest tightness and breath holding with each episode of strenuous exercise since the age of 15 was admitted; his symptoms were relieved after rest. Transthoracic echocardiography (TTE) was conducted, and the results suggested malformation of the bicuspid aortic valve (BAV) with stenosis; no specific treatment was performed. In August 2021, the patient visited our hospital after feeling chest tightness and

breath holding with slight activity. These symptoms were accompanied by a fever with the highest temperature being 38.5°C. There were no chills and chills, no cough and sputum. The results of a physical examination of his heart at admission were as follows: The heart rhythm was uniform, a soft grade II/6 systolic murmur could be heard in the second intercostal space on the left edge of the sternum, and there were no pericardial friction sounds. The results of laboratory examinations were as follows: The white blood cell count was $9.61 \times 10^9/L$, neutrophil count was $6.25 \times 10^9/L$, hemoglobin was 157 g/L, platelet count was $274 \times 10^9/L$, and ultrasensitive C-reactive protein was 27.5 mg/L. The calcitoninogen was 0.06 ng/mL, hematocrit was 27 mm/h, and rheumatoid factor was 16 IU/mL. The hepatic and renal function, as well as the urine routine test, were normal. The results of TTE were as follows: BAV with stenosis, septal hypertrophy, and widening of the aortic ascending segment existed. Strong echogenicity was visible at the root of the aortic valve. The results of the transesophageal echocardiography (TEE) showed BAV with severe stenosis and strong echogenicity at the aortic valve root; the possibility of an inflammatory mass could not be excluded (Figures 1 and 2). There was no significant abnormality in the electrocardiogram (ECG), chest computed tomography (CT), abdominal ultrasound, and cranial magnetic resonance imaging (MRI). The diagnosis of infective endocarditis (IE), severe aortic stenosis, and dilatation of the ascending aorta was considered with the combination of the clinical manifestations, physical examination, and laboratory tests. Vancomycin (1 g, q12h) plus ceftriaxone (2 g, qd) were administered empirically as intravenous anti-infection therapy. The patient still had recurrent fever after more than 10 days of treatment, and the blood culture (the bilateral double vials) was negative four consecutive times. The presence of uncommon pathogens was considered highly likely, thus mNGS in the blood sample was conducted to assist the diagnosis. Two days after sending for the mNGS, the results suggested the existence of *C. burnetii* with a blood cell layer sequence number of 134 and a plasma layer sequence number of 1 (Figure 3). The diagnosis was considered to be Q fever endocarditis, and therefore, the Q fever serological antibody assay was conducted (positive for the Q fever Phase II IgG). Doxycycline (100 mg, every 12 hours) was then administered intravenously in combination with hydroxychloroquine (200 mg, three times a day) orally, and the temperature of the patient returned to normal after one week of treatment. In October 2021, the patient underwent a mechanical aortic valve replacement with an ascending aortic replacement under general anesthesia. The intraoperative observations were as follows: The ascending aorta was significantly thickened, with a diameter of approximately 5.0 cm, together with the thin aortic wall. BAV, severe calcification, and thickening of the valve leaflets existed, resulting in valve stenosis with an incomplete closure,



Figure 1 The results of transesophageal echocardiography.



Figure 2 The results of transesophageal echocardiography.

Sequence number	The genus information		The species information			
	Genus name	Sequence number	Species name	Sequence number	Coverage	Relative abundance
1-The blood cell layer	Coxiella	134	Coxiella_burnetii	134	18885 bp 0.90%	100.0%
<div><div><div>The distribution map of the detected genome location</div><div></div></div></div>						
2-The plasma layer	Coxiella	1	Coxiella_burnetii	1	374 bp 0.02%	100.0%

Figure 3 The results of metagenomic next-generation sequencing in blood.

and punctate vegetation was visible. The resected valve with lesions was sent for pathological examination and mNGS. The results of mNGS in the cardiac tissue revealed the existence of *C. burnetii* with the sequence number of 214,080 (Figure 4). The combination therapy of doxycycline with hydroxychloroquine was continued postoperatively, and the patient was followed up for more than one month without the occurrence of fever and without symptoms of chest



Figure 4 The results of metagenomic next-generation sequencing in cardiac tissues.

tightness and breath holding. The TTE examination suggested good prosthetic valve function and smooth blood flow in the prosthetic vessels.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Yantai Yuhuangding Hospital. The consent from the patient for the publication of the case was obtained.

Discussion

Q fever is a globally spread zoonotic disease caused by the *C. burnetii* infection. The clinical manifestations of Q fever are diverse; while some patients have severe manifestations of acute or chronic infection, others have mild clinical signs and symptoms, often without, or only low, fever.³ Q fever often causes endocarditis, however, this diagnosis is currently challenging and requires a combination of clinical, microbiological, and/or imaging findings. In the present study, a patient was diagnosed with Q fever endocarditis combined with valvular heart disease, which is a high risk for the development of Q fever.² A heart valve vegetation was revealed in the echocardiogram conducted after admission and the possibility of IE was considered. However, the empirical anti-infection therapy was ineffective, with four consecutive negative results in the blood cultures. Therefore, samples were sent for mNGS in the blood to clarify the pathogenic diagnosis. Unbiased detection of a wide range of pathogenic microorganisms can be achieved through mNGS (including viruses, bacteria, fungi, and parasites) through shotgun sequencing of DNA or RNA from clinical samples, regardless of the success culture of the clinical sample, as long as the samples contain detectable DNA or RNA.⁴ The results of the mNGS provided a direction for pathogenic diagnosis. Samples were then sent for the Q fever serological antibody assay, which showed the existence of a positive Q fever phase II antibody.

Although vegetation was found in the heart valves during the TTE and TEE in the present case, vegetation was rarely found in most patients with Q fever endocarditis using cardiac ultrasonography.⁵ This was because the vegetation in

Q fever endocarditis, unlike those in bacterial endocarditis, manifested as endothelial-covered nodules on the valves, which were often small and difficult to be detected and were often missed in diagnosis. As with the diagnosis of endocarditis caused by other pathogens, the sensitivity of TEE in the diagnosis of Q fever endocarditis is higher than that of TTE.⁶ Surgical replacement of the injured valve is often necessary for patients with Q fever endocarditis due to hemodynamic reasons. However, the histologic manifestations of the tissue obtained intraoperatively from patients with Q fever endocarditis are nonspecific with the inclusion of significant fibrosis and calcification, mild inflammation and angiogenesis, and the absence or presence of only small vegetation. These pathological features are easily confused with noninfected degenerative valve lesions.⁷ While the DNA of the *C. burnetii* could be detected in tissue by mNGS.

Combined therapy of hydroxychloroquine (hydroxychloroquine 600 mg orally, once a day or 200 mg, three times a day) and doxycycline (100 mg orally, twice a day) is preferred in patients with Q fever endocarditis for a minimum duration of 18 months. Minocycline may be applied in patients who cannot tolerate doxycycline (eg, the occurrence of nausea). Some case reports have found that the combination of doxycycline with rifampin, doxycycline, and quinolones is also effective. A retrospective study compared the therapeutic effects of hydroxychloroquine plus doxycycline with doxycycline plus a quinolone and showed that the former had better clinical efficacy.⁸ In the treatment of Q fever endocarditis, the dose of hydroxychloroquine is relatively high and is prone to result in ocular toxicity. The retina should be examined once before administration and every six months thereafter to determine the occurrence of early signs of toxicity associated with hydroxychloroquine, such as corneal deposition and retinopathy.

Conclusion

In recent years, with the increase in the immune-compromised population, it is more difficult to clarify the etiology of IE by traditional methods, especially in patients with negative results in blood cultures, in whom Q fever endocarditis is common. The application of mNGS could provide a rapid and accurate assay in clinical diagnosis and play a decisive role in the pathogenetic diagnosis of some infectious diseases.⁹

Funding

This study was supported by effect of TLR2 on dectim-1 expression in human bronchial epithelial cells infected with *Mycoplasma pneumoniae* (No. 2017WS165).

Disclosure

The authors declare that there is no conflict of interest in this work.

References

1. Larson PS, Espira L, Grabow C, et al. The sero epidemiology of *Coxiella burnetii* (Q fever) across livestock species and herding contexts in Laikipia County, Kenya. *Zoonoses Public Health*. 2019;66(3):316-324. doi:10.1111/zph.12567.
2. Straily A, Dahlgren FS, Peterson A, Paddock CD. Surveillance for Q Fever Endocarditis in the United States, 1999-2015. *Clin Infect Dis*. 2017;65:1872. doi:10.1093/cid/cix702
3. Hartzell JD, Wood-Morris RN, Martinez LJ, Trotta RF. Q fever: epidemiology, diagnosis, and treatment. *Mayo Clin Proc*. 2008;83:574. doi:10.1016/S0025-6196(11)60733-7
4. Simmer PJ, Miller S, Carroll KC. Understanding the promises and hurdles of metagenomic next-generation sequencing as a diagnostic tool for infectious diseases[J]. *Clin Infect*. 2015;2:548
5. Elzein FE, Alsherbeeni N, Alnajashi K, et al. Ten-year experience of Q fever endocarditis in a tertiary cardiac center in Saudi Arabia[J]. *Int J Infect Dis*. 2019;88:21-26. doi:10.1016/j.ijid.2019.07.035
6. Anderson A, Bijlmer H, Fournier PE, et al. Diagnosis and management of Q fever—United States, 2013: recommendations from CDC and the Q Fever Working Group. *MMWR Recomm Rep*. 2013;62:1.
7. Lepidi H, Houpiqian P, Liang Z, Raoult D. Cardiac valves in patients with Q fever endocarditis: microbiological, molecular, and histologic studies. *J Infect Dis*. 2003;187:1097. doi:10.1086/368219
8. Raoult D, Houpiqian P, Tissot DuPont H, et al. Treatment of Q fever endocarditis: comparison of 2 regimens containing doxycycline and ofloxacin or hydroxychloroquine. *Arch Intern Med*. 1999;159:167. doi:10.1001/archinte.159.2.167
9. Wilson MR, Naccache SN, Samayoa E, et al. Actionable diagnosis of neuroleptospirosis by next-generation sequencing[J]. *N Engl J Med*. 2014;370(25):2408-2417. doi:10.1056/NEJMoa1401268

Infection and Drug Resistance**Dovepress****Publish your work in this journal**

Infection and Drug Resistance is an international, peer-reviewed open-access journal that focuses on the optimal treatment of infection (bacterial, fungal and viral) and the development and institution of preventive strategies to minimize the development and spread of resistance. The journal is specifically concerned with the epidemiology of antibiotic resistance and the mechanisms of resistance development and diffusion in both hospitals and the community. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/infection-and-drug-resistance-journal>