Chronic Q Fever Endocarditis in an Omani Child: The First Pediatric Case Report from Oman

Hanaa A. AlAraimi[1], Khalid Al-Alawi[2], Amina K. Al-Jardani[1], George Paul[2,3], Nashat Al-Sukaiti[2], Abdullah Al-Farqani[2,4] and Amal S. Al-Maani[2,3*]

[1]Department of Microbiology, Royal Hospital, Muscat, Oman
[2]Department of Pediatrics, Royal Hospital, Muscat, Oman
[3]Division of Pediatric Infectious Diseases, Royal Hospital, Muscat, Oman
[4]Division of Pediatric Cardiology, Royal Hospital, Muscat, Oman

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ABSTRACT

Q fever endocarditis is the most common presentation of chronic infection of *Coxiella burnetii,* but it rarely occurs in the pediatric age group. We report the first case of Q fever endocarditis in an Omani child. The affected 11-year-old female lives in the Al Batinah governorate in the north of Oman and was known to have congenital heart disease. She presented with features of chronic blood culture-negative endocarditis. The *C. burnetii* infection was confirmed with the indirect immunofluorescence assay. The patient responded well to a combination of doxycycline and hydroxychloroquine therapy.

Q fever is a zoonotic disease found worldwide and is caused by *Coxiella burnetii*, an obligate intracellular small gram-negative bacillus. Cattle, sheep, and goats are the primary reservoirs.[1] It is usually transmitted from farm animals by inhaling contaminated aerosols and dust. Other rare modes of transmission are ingestion (mainly drinking raw milk), transplacental, blood transfusion, and arthropod-borne transmission.[2]

There have been few pediatric cases of Q fever reported. In children, the disease can be asymptomatic, cause self-limited influenza-like illnesses, pneumonia, hepatitis, or manifest as serious infections such as chronic endocarditis.[1,3] Here, we present the first diagnosed pediatric case of Q fever endocarditis reported from Oman.

CASE REPORT

An 11-year-old Omani female residing in the North Al Batinah governorate known to have congenital heart disease was admitted for cardiac catheterization in January 2012. Her primary cardiac condition was a transposition of the great vessel, ventricular septal defect, and pulmonary stenosis. She underwent a Rastelli procedure with a conduit connecting the right ventricle to the pulmonary artery at the age of 7 years. On admission, the patient appeared pale and was found incidentally to have an enlarged liver (5 cm below costal margin) and spleen (4 cm below costal margin). The patient was noted to have several laboratory abnormalities, including hemoglobin of 5.4 g/dL with microcytic hypochromic picture with normal platelet and white cell counts. Her erythrocyte sedimentation rate was 61 mm/h (high) and C-reactive protein was 46.3 mg/L (high). Urine microscopy showed microscopic hematuria. On the patient's second day of admission, she had a high-grade fever with no clear clinical focus. Four blood cultures in two consecutive days were taken, and she was started on piperacillin-tazobactam and vancomycin empirically. Infective endocarditis was suspected, but the initial transthoracic echocardiography did not show any evidence of vegetation. The child continued to spike a fever despite antibiotics 3–4 times daily, and her blood cultures remained negative after prolonged incubation.

Further work-up was completed, which included a smear for malaria and serology for cytomegalovirus, Epstein-Barr virus, *Brucella*, *Bartonella*, *Leishmania*, and *C. burnetii*. Bone marrow examination was done on day 10 of admission and did not show any evidence of malignancy. Screening tests for autoimmune and connective tissue diseases were unremarkable. At that time, the result of qualitative Q fever serology (Virion/Serion ELISA, Wurzburg, Germany) came

*Corresponding author: ✉amalsaifalmaani@gmail.com

positive for both immunoglobulin G (IgG) and IgM, so a confirmatory quantitative tests indirect immunofluorescence (IIF) assay for phase I and II IgM and phase I IgG were sent to Pasteur Cerba Laboratory in France. Polymerase chain reaction for Q fever was not available. All other serological tests were negative. Further history was taken regarding farm animal exposure, and the patient's father gave a clear history of contact with goats upon the patient's visits with her grandmother. Though it was never documented, the father added that she had a fever on and off for the past few months. Repeated transthoracic echocardiography yielded no results, so a transesophageal echocardiogram (TEE) was performed and showed vegetation at the ventricular septal defect pedunculated to the left ventricular outlet. Abdominal computed tomography scan showed multiple small lesions in the spleen suggestive of splenic abscesses. In light of the TEE report, negative blood culture, and positive Q fever serology, a diagnosis of Q fever endocarditis was highly considered. At that point, the child was started on doxycycline and hydroxychloroquine. The fever improved within two days, and the child was discharged home on seventh day of admission with oral antibiotics. Later, the report from Pasteur Cerba Laboratory in France confirmed a chronic *C. burnetii* infection with titers of phase I IgM antibodies of 1024, phase I IgG antibodies of 1024, and phase II IgM antibodies of < 32.

Upon follow-up, the patient remained afebrile, and her spleen size regressed to normal after six months of therapy. TEE showed the disappearance of the previous vegetation after one year of therapy. An abdominal ultrasound showed a resolution of splenic abscess. Q fever antibody titers gradually decreased over three years [Table 1]. The patient completed two years and eight months of antibiotics. During that time, she was followed by an ophthalmologist and evaluated for the development of ocular toxicity related to hydroxychloroquine. She tolerated therapy well and experienced no adverse effects.

DISCUSSION

Q fever in Omani children has not been reported previously, and the epidemiology of this zoonotic infection in the country has not been established. In 2000, Q fever was documented for the first time in Oman in two adult patients, one with chronic pericarditis and the other with acute pneumonia.[4] The highest prevalence rates of Q fever have been reported from the Netherlands, France, and the Middle East. Worldwide, Q fever in children has been rarely reported. However, the disease may be underdiagnosed as children are less frequently symptomatic than adults following infection, and may have milder forms of the disease.[1,3] The diagnosis of the child in our case was delayed and doubted even after the initial qualitative serology came back positive due to the rarity of this infection in children and that zoonotic distribution in Oman is not well defined.

Endocarditis is the most common presentation of chronic Q fever (60–70% of cases).[2] It represents 3–5% of all cases of endocarditis,[2,5] and is the main etiology of blood culture-negative endocarditis (up to 57.3%).[6] Other forms of chronic Q fever that have been reported in the literature are osteomyelitis,[7] central nervous system involvement, and chronic hepatitis.[8] The risk of transformation from acute Q fever to endocarditis is estimated to be 7.6% in the general population and 39% among patients with underlying valvular defects.[9] Risk factors for progression from acute to chronic Q fever endocarditis are preexisting valvular disease, vascular prosthesis or aneurysm, immunocompromised condition, or pregnancy.[10] Mortality from Q fever endocarditis is estimated to be 10–24% with the appropriate treatment.[2,11]

The clinical presentation of Q fever endocarditis is non-specific as seen in this case. Many patients present with symptoms of heart failure, valve dysfunction, or with constitutional symptoms, including fever, malaise, weakness, weight loss, fatigue, chills, anorexia, and night sweats.[2,11] Other reported

Table 1: Serial of follow-up Q fever quantitative titer.

Date Antibodies	Feb 2012	Aug 2012	Jun 2013	May 2014	Feb 2015
Phase II IgM abs	< 32	< 32	< 32	< 32	< 32
Phase I IgM abs	1024	1024	512	256	128
Phase I IgG abs	1024	1024	128	128	64

Ig: immunoglobulin; abs: antibodies.

manifestations are hepatomegaly, splenomegaly, clubbing, purpuric rash, and septic emboli.[11] Our patient had fever, hepatomegaly, splenomegaly, and splenic abscess indicating septic emboli. The routine lab investigation may show leukocytosis, leucopenia, increased transaminase level, thrombocytopenia, anemia, increased creatinine level, and elevated sedimentation rate.[9]

In children, vegetations are rarely seen by transthoracic cardiac echocardiography. Cardiac vegetation is visible on the echocardiogram in only 12% of patients and is often small. TEE is more sensitive than transthoracic echocardiography.[1,2,9] In our case, two TTEs were negative, and only when TEE was done was the vegetation seen to confirm the suspected endocarditis.

Because clinical diagnosis and laboratory culture techniques are difficult, the diagnosis of Q fever normally relies on serological methods. Indirect IIF assay is the reference method for the diagnosis of Q fever.[1,2,9] *C. burnetii* exists in two antigenic phases, phase I and phase II, which help in differentiating acute from chronic infection. Phase I is the virulent, highly infectious form that undergoes a transition to phase II. In acute infection, the phase II antibody response to *C. burnetii* appears first and is higher than the phase I antibody response.[1,2] Phase II IgG titers > 200 and IgM titers > 50 are the cut-off value for diagnosis of acute Q fever on a single serum.[1,2] Chronic Q fever is diagnosed on the basis of a phase I IgG titer > 800.

Q fever endocarditis is difficult to treat and often requires prolonged and combination therapy. The recommended treatment regimen is doxycycline and hydroxychloroquine or doxycycline with quinolone. Treatment should continue for at least 18 months for native valve infections and at least 24 months for prosthetic valve infections.[1,2] The Centers for Disease Control and Prevention recommends monthly serologic testing for *C. burnetii* phase I and II IgG and IgM antibodies and monthly clinical evaluations during treatment for chronic Q fever.[1] Others recommend serological testing once a month for the first six months of treatment, then every three months to assess the duration of treatment.[11] Because of potential retinal toxicity from long-term use of hydroxychloroquine, a baseline ophthalmic examination should be performed before treatment and every six months thereafter.

Our patient had a clear history of exposure to goats when visiting her grandmother. She presented with clinical picture keeping with blood culture-negative infective endocarditis, and the modified Duke criteria for infective endocarditis was met with two major and two minor criteria.[12] All other causes of infective endocarditis were ruled out, and the culture remained negative. The IIF assay titer for phase I antigen was > 1:800, and this fits the diagnostic criteria for chronic Q fever. A TEE showed vegetation, which confirmed the diagnosis of Q fever endocarditis. The patient responded well to doxycycline and hydroxychloroquine. Her fever disappeared two days following, and hematuria resolved after six months. There was regression of hepatosplenomegaly after the first week of treatment and a complete disappearance after six months of therapy. After a year of treatment, the follow-up serology showed a decrease in the phase I titer [Table 1].

The zoonotic map for Q fever in Oman is a project that the Ministry of Agriculture, Fisheries, and Water Resources is working to finalize. Once it is published, the map will help to suspect diagnosis in patients coming from regions where the disease burden in livestock is high.

CONCLUSION

Q fever is an underdiagnosed infection. It is underdiagnosed more often in children than adults. The diagnosis of Q fever endocarditis, as this case demonstrates, should be considered in any patient with blood culture-negative endocarditis and compatible epidemiological and exposure histories.

Disclosure
The authors declared no conflicts of interest.

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