Case Report

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Coxiella Burnetii endocarditis in a child with operated congenital heart disease who presented with fever of unknown origin

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Summary

Q fever is a zoonotic infection caused by Coxiella Burnetii. Although it is usually asymptomatic, acute form of disease may change from flu-like illness to severe pneumonia. Chronic form may present with vascular disease or endocarditis. A 6-year-old female patient from Sudan followed with the diagnosis of pulmonary atresia and ventricular septal defect was referred to our department because of stenosis in the conduit placed to right ventricular outflow during Rastelli operation performed in Sudan. Six months ago in Jordan, stenting was performed for conduit stenosis, but was unsuccessful. Because of long lasting fever she was treated for culture negative endocarditis in Sudan. In physical examination fever and hepatosplenomegaly were present. Laboratory findings revealed anemia, leukopenia, Coombs' positivity, hypergamaglobulinemia and positive anticardiolipin antibodies but blood cultures were negative. Different antibiotic protocols were administered for culture-negative endocarditis for 2 months, but fever persisted. On 67. day of hospitalization positive antibody titers for Coxiella Burnetii were detected and doxycycline and hydroxychloroquine were started. Here, a case of chronic Q fever due to Coxiella burnetii which is a rare cause of culture-negative endocarditis is presented. *(Turk Arch Ped 2013; 48: 339-341)*

Key words: Endocarditis, operated congenital heart disease, Q fever

Introduction

Q fever is a zoonotic infection caused by Coxiella burnetii which is an obligatory intracellular gram negative organism (1). It is observed more commonly in risk groups who are in contact with animals. Q fever has a wide spectrum of hosts including mainly humans, ruminants (cattle, goat, sheep), cats, dogs and reptiles. Humans are usually infected by inhalation of contagious aerosols scattered around with stools, milk, placentas and body fluids of infected animals (2). Conditions including cardiac valve lesions and vascular anomalies may predispose to chronic Q fever. Chronic forms are usually observed as endocarditis and vascular diseases (3). Here, a patient who developed endocarditis related with chronic Q fever on the background of congenital heart disease was presented as the first case reported from Turkey.

Case

A 6-year old female patient who underwent Rastelli operation two years ago and who was being followed up with the diagnoses of pulmonary atresia and ventricular spetal defect (VSD) in Sudan was referred to the pediatric cardiology clinic of our hospital because of stenosis in the conduit. On physical examination her general status was moderate and she appeared weak. Her body temperature

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was 39 C°. She had a midsternal scar related with the operation performed and a 3/6 systolic murmur on the left 2-3th intercostal space. The liver was palpable 10 cm below the costa and the spleen extended up to the inguinal region. Transthoracic echocardiography revealed stenosis in the conduit placed between the right ventricle and pulmonary artery and peripheral stenosis in the left and right pulmonary arteries. No vegetation was observed. Abdominal ultrasonography revealed hepatosplenomegaly. No abscess was observed in the myocardium and/or around the valve on cardiac magnetic resonance imaging. Laboratory tests were as follows: WBC:7690/ mm^3, hemoglobin: 10 gr/dL, platelets :139x10^3 /mm^3, hepatic and renal function tests: normal. Microscopic hematuria was found in urinalysis. Among acute phase reactants, erythrocyte sedimentation rate was found to be 32 mm/h and CRP was found to be 15 mg/lt. Direct and indirect Coombs tests were found to be positive. Mycoplasma pneumonia antibodies and cold agglutinins were found to be negative. Immunoglobulin values were as follows: Ig G : 2640 mg/dL, IgM: 370 mg/dL , IgA: 12,6 mg/dL , IgE: 58 mg/dL. Serologic tests revealed that HBs antigen, anti HBs, anti HIV, anti HCV, HIV RNA (PCR), anti CMV IgG, Anti CMV IgM, EBV VCA IgG, EBV VCA IgM, EBV EBNA, anti toxoplasma IgM, Anti toxoplasma IgG were negative. Serological tests for parasitic and bacterial infections revealed that Tuberculosis, Brucella, Toxocara canis, Leishmania, Entamoeba histolytica, Schistosoma, Borrelia burgdorferi, Francisella tularensis, Fasciola hepatica were negative. Tests for rheumatic etiology were as follows: RF:1420:İU/l, C3: 1.42 g/L (0.83-1.77), C4:0.92 g/L (0.12-0,4), ANA, Anti-DNA, c-ANCA(PR3), p- ANCA(MPO), Anti-Scl 70, Anti SSA-SSB negative, anticardiolipin IgM positive, anticardiolipin IgG negative. Multiple blood and urinary cultures were negative. Bone marrow culture was also negative and no malign cell was found. Thick blood smear for malaria was negative. Antimalarial antibodies (France Pasteur Institute) were found to be negative. Bacterial endocarditis was considered because of resistant fever, hepatosplenomegaly and Coombs positivity. Different antibiotics and antimalarial drugs were given (ceftriaxone for 10 days, ceftriaxone and amikacin for 24 days, meropenem, lipozomal amphotericin B and teikoplanin for 10 days, armethene lumefantrine, mefloquine and quinine for 13 days). The patient's fever continued intermittently. Although the test was negative antimalarial treatment was given to the patient, since she was coming from Sudan, but the fever could not be controlled.

On the 67th day of the symptoms, Q fever indirect fluorescence antibody (IFA, Vircell SLR, Granada, Spain) test performed in Refik Saydam Hygiene Center revealed that Phase II IgG titer was measured to be 1/262144, IgM titer was measured to be 1/96, Phase II+Phase I IgG titer was measured to be 1/65536, Phase I IgG titer was measured to be 1/87381 and this was compatible with chronic infection. Coxiella Burnetti PCR was found to be positive. Doxycycline (4.4 mg/kg/day in 2 doses) and hydrocortisone (7 mg/kg/day in 2 doses) treatment was started. On the third day of treatment, fever subsided and one month later a marked reduction was observed in the liver and spleen. Treatment was planned as 18 months.

Discussion

Endemic Q fever is a zoonotic disease which is characterized with nonspecific findings including sudden fever, shiver, malaise, headache and loss of appetite and which is caused by a rickettsia (Coxiella Burnetii) (1). The clinical findings vary in acute Q fever. It frequently occurs as a self-limiting nonspecific influenza-like pyretic disease and is easily missed. In patients with more severe findings, it may be observed as atypical pneumonia or acute hepatitis. Chronic forms are manifested as endocarditis and vascular diseases. While the disease mostly has an asymptomatic or self-limiting course, pictures which require hospitalization may also occur in 2% of the patients (1,2,3,4). Some conditions including pregnancy, immune failure, cardiac valve lesions and vascular anomalies may lead to predisposition to chronic Q fever. Anticardiolipin antibodies which are observed in the course of chronic Q fever have been reported to be the cause of abortus in pregnant women (5). Endocarditis is the most common form of chronic Q fever and constitutes 60-70% of all cases and 3-5% of all cases with endocarditis. Endocarditis develops in .076% of the cases during acute attack. The clinical and echocardiographic findings are different from typical acute bacterial endocarditis, the blood culture is negative and its diagnosis delays (5,6). Presence of a history of open heart operation, presentation from Sudan and the fact that the etiology of fever could not be elucidated despite investigations performed in different external centers suggested endocarditis caused by rare agents.

Coxiella Burnetii is a microorganism which shows phase change and loses some of the surface antigens in the culture setting. Phase I is the virulent phase and causes to infection in humans and animals. Phase II is the avirulent phase which occurs after a series of stages in the laboratory setting. Phase I and Phase II organisms are different from each other in terms of amino acid, neutral sugar content, immunogenic surface antigens, cell density and resistance to phagocytosis (7). In acute infection, primarily IgM antibody develops against phase II antigens in a few days and afterwards IgA and IgG antibodies develop. In the healing period, IgM antibody starts to develop against phase I antibodies and is maintained at a low level for two years after the healing period (8,9). If phase II IgG titer is >200 and phase II IgM titer is >50, a diagnosis of Q fever is made. If phase I IgG titer is >800, a diagnosis of chronic Q fever is made. According to the modified Duke

criteria, the major criterion for Q fever endocarditis is a phase IgG antibody titer of >1:800 for Coxiella Burnetii. The minor criteria include predisposition, fever, vascular events, immunological events and microbiological evidence (11). In our patient, phase I IgG antibody titer was found to be >1: 1/87381 for Coxiella Burnetii which was a major criterion and minor criteria included heart problem which caused to predisposition, fever, rheumatoid factor positivity among immunological events and microscopic hematuria which showed glomerulonephritis. Since one major and three minor cirteria which were required for a definite diagnosis were met, a diagnosis of endocarditis was made.

If chronic Q fever endocarditis is not treated, the moratlity rate is high. The mortality rate is 10% despite appropriate treatment. Therefore, early diagnosis and initiation of antibiotic treatment without losing time is important (12). However, the mean time of delay for diagnosis in chronic Q fever endocarditis has been reported to be six months (13). In our patient, the time of delay for diagnosis was 2,5 months which was below the average.

In the literature screening, we could find no case of chronic Q fever endocarditis caused by Coxiella Burnetii published in Turkey. According to the literatur survey performed by Yıldırmak et al. (14) in 2010, 112 acute cases caused by Coxiella Burnetii had been defined in Turkey including their own cases. 8 of these cases were pediatric cases. 92 of the remaining 104 adult cases were published between 1948 and 1951. Fifty of these were pneumonia cases defined in a single center in a period of 10 years and 21 were patients defined in a village epidemia. Gender distribution was balanced. The distribution of clinical forms was as follows: 71 cases of penumonia, 8 cases of hepatitis and 2 cases of hepatitis accompanying pneumonia.

Conclusively, congenital heart diseases and rheumatic valve damages are the most significant risk factors for infective endocarditis. Cardiac surgery and invasive interventions increase the risk further. Endocarditis should absolutely be included in the differential diagnosis in each case of fever of unknow origin, if the diagnosis cannot be made in a few days. In addition, it should be kept in mind that Coxiella Burnetii is responsible of 75% of the cases of culture negative endocarditis in endemic regions.

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