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Case report

Chronic Q fever: A missed prosthetic valve endocarditis possibly for years

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ABSTRACT

Chronic *Coxiella burnetii* endocarditis usually develops in people with underlying heart disease and accounts for 60–70% of chronic Q fever. Onset is generally insidious and manifestations are atypical. The authors report a case of *Coxiella burnetii* prosthetic valve endocarditis in a 53 years- old patient with recurrent mechanical valve dehiscence on mitral position. He lived in a rural area with sheep and goats on the surroundings. During a 9 year- period, he was submitted to three cardiac mitral valve surgeries two of which with no Q fever diagnosis suspicion. Diagnosis was based on a positive serology test (Indirect imunofluorescence). Treatment consisted in a combination of prolonged course of hydroxychloroquine plus doxycycline and surgical replacement of the mitral valve, with a favorable outcome. With this case report, the authors pretend to highlight the not always expected diagnosis of Q fever endocarditis. If not considered, Coxiella burnetii endocarditis may lead to multiple cardiac surgeries, greater morbidity and potentially death.

Introduction

Caused by *Coxiella burnetii,* an obligate intracellular Gram-negative bacterium, Q fever can be acute or chronic. Long-term sequelae are beginning to gain acceptance as a third category of this zoonotic disease [1]. Endocarditis usually develops in people with underlying heart disease and accounts for 60–70% of chronic Q fever cases [2]. Onset is generally insidious and manifestations are atypical as fever can be absent [3], and vegetations can be unapparent or small [4,5]. Additionally, exposure to *Coxiella burnetii* may be difficult to ascertain.

The authors report a case of a prosthetic valve endocarditis caused by *Coxiella burnetii* in a 53 year- old patient with recurrent mechanical valve dehiscence. We consider this case of major importance to highlight that even if endocarditis is the most common manifestation of chronic Q fever it is still a rare disease and can be difficult to diagnose as its clinical course is variable.

Case report

A case of a 53-year old patient with a past history of transfusional hepatitis C and a splenectomy at the age of 23, who was admitted in the Infectious Diseases Department of a Portuguese Hospital in October 2015 because of a recent onset of fever, dyspnea, fatigue and non productive cough.

The patient's previous relevant medical history started in June 2004, at the age of 41 years old, when he presented with heart failure symptoms due to mitral stenosis. In October 2005 mitral-valve replacement with a mechanical Medtronic valve was performed.

Five months later (in March, 2006), patient began to have anorexia, fatigue, progressive dyspnea on exertion, paroxysmal nocturnal dyspnoea and peripheral edema.

Transesophageal echocardiogram revealed a severe mitral insufficiency secondary to dehiscence of the prosthesis and a new intervention was performed in August 2006 to correct the leak without valve replacement.

Six months later he was again admitted for progressively worsening dyspnoea, asthenia and palpitations with one month duration and fever (38–39 °C) in the previous week. Atrial

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fibrillation was detected. Transesophageal echocardiogram revealed slight dilation of the left cavities and right atrium, with preserved ejection fraction and new partial dehiscence of the prosthesis with elevation of the transprothesic gradient (43/15 mmHg) causing severe mitral insufficiency and severe pulmonary hypertension (>100 mmHg). Blood tests revealed leukocytosis and C-reactive protein elevation. A diagnosis of culture negative endocarditis was presumed and empirical antimicrobial therapy was started with rifampin (300 mg po tid), vancomycin (500 mg bid IV adjusted to blood levels) and gentamicin (500 mg/day IV).

In March 2007 he underwent a third surgical intervention: mitral valve replacement with St Jude 27 prosthesis and tricuspid annuloplasty with a Medtronic ring. Microbiological examination of the excised valve was negative. No pathogen had grown in the collected blood cultures. He completed 2 weeks of gentamicin and 4 weeks of vancomycin and rifampin and was started on hypocoagulation with warfarin for his permanent atrial fibrillation. The outcome was favorable.

In October 2015 (8 years later), patient was referred to the emergency room of a peripheral hospital with a history of two weeks duration of persistent non productive cough, myalgia, fever and worsened dyspnea on exertion. He denied orthopnea, paroxysmal nocturnal dyspnea, thoracic pain, vomiting, anorexia or other gastrointestinal or urinary symptoms.

Concerning the patient epidemiological context, he was retired (used to work in metal processing), lived in a rural area with sheep and goats on the surroundings but had no pets or any farm animals in his house. He denied unpasteurized dairy products consumption and used only bottled water. He also denied high risk sexual exposures. He reported neither recent travel nor contact with ill persons. Medications taken on a daily basis included warfarin, carvedilol (9.375 mg/day), ramipril (1.25 mg/day), furosemide (20 mg/day), digoxin (0.125 mg/day except weekends).

On physical examination, patient was febrile (temperature of 38,2 °C), blood pressure was 91/62 mmHg, pulse 80 beats per minute, room air peripheral O2 saturation of 100%, pulmonary auscultation was normal and cardiac auscultation revealed an irregular rhythm with a grade III/VI systolic murmur heard at the base and apex. Dentition was poor, but with no abscesses. No peripheral oedema, splinter haemorrhages, Osler's nodes or Janeway's lesions were present. The remaining physical examination was unremarkable.

Blood workup revealed a haemoglobin 9 g/dL, platelets 293.000, leukocytes 10, 95 × 10^4, 59% neutrophils, 15% lymphocytes, C-reactive protein 29,6 mg/L. Aspartate aminotransferase 129 UI/L; alanine aminotransferase 36 UI/L, alkaline phosfatase 63 UI/L, gamaglutamil transferase 32U/L, Lactate dehydrogenase 2822 UI/L, total bilirrubin 2,63 mg/dL. Iron 79 ug/dL, iron binding capacity 232 ug/dL, ferritin 11 ng/mL, haptoglobin <0.8 g/dL, Vitamin B12 502 pg/mL, Folic acid 5.4 ng/mL. Renal function was within normal range. Antinuclear, anti-smooth muscle, antimitochondrial anti- dsDNA and anti-histone antibodies were all negative. Ceftriaxone 2 g/daily was started and he was admitted on the Internal Medicine Department of another Hospital for study. An Infectious Diseases Consultation was called for case discussion and complementary exams were suggested, namely: *Brucella* spp. (*Wright test*) and *Coxiella burnetti* serologies.

The electrocardiogram showed atrial fibrillation, 67 beats per minute. The Chest X-ray revealed a right pleural effusion. The transesophageal echocardiogram revealed: dilation of the left cavities, preserved systolic function with an ejection fraction of 54%, mild aortic insufficiency and mitral valve prosthesis with two regurgitant jets with a moderate periprosthetic leak. Blood cultures collected did not isolate any pathogen. Serology for *Brucella* spp. was negative.

Serologies for *Coxiella burnetti* were positive: IgG antibodies to phase I were 1:32 768 and IgG antibodies to phase II was 1:16 384. IgM antibodies to phase I was 1:512 and IgM to phase II was 1:256. Polymerase chain- reaction (PCR) for *Coxiella burnetti* was positive in the blood. Patient was transferred to our hospital.

The diagnosis of Chronic Q fever endocarditis and haemolytic anemia secondarily to periprosthetic leak were presumed. Doxycycline (100 mg orally bid) plus hydroxychloroquine (600 mg/day) were started. Surgery was performed in December 2015 with valve replacement by a mechanical prosthesis ST Jude n° 27. The patient was discharged one week after surgery with the indication to complete therapy with doxycycline plus hydroxychloroquine for at least 24 months. During follow up no events were reported and 8 months later he is still asymptomatic (no signs or symptoms of heart failure, serial echocardiography showing a preserved integrity of the valve).

Discussion

Q fever is a worldwide zoonosis and the most common sources of human infection are farm animals such as cattle, goats and sheep, but also cats, rabbits and dogs can be responsible for infection in an urban context [6]. These mammals, when infected, can shed the desiccation- resistant form of the organism in urine, faeces, milk and, especially, birth products [7]. Infection in humans results from inhalation of contaminated aerosols from these specimens [8]. Contact with animals, even if indirect, is important to suggest the diagnosis of Q fever [2]. In Europe, Q fever cases are more frequently reported in spring and early summer. They may occur at all ages, but are more frequent in men. *Coxiella burnetii* is endemic in Portugal [9]. Mortality occurs in 1–11% of patients with chronic Q fever [10].

The clinical picture is very unspecific but it is known that chronic infection can develop month or years after acute Q fever [11], which can be asymptomatic. The most common manifestation of chronic disease is endocarditis and *C. burnetii* was the leading cause of negative blood culture prosthetic- valve endocarditis in one study of men less than 65 years old. Symptoms began gradually as long as 1–20 years after initial infection [12]. Most cases involve the aortic or mitral valve in patients with pre-existing valvular disease or prosthetic valves. Infection can be very indolent without fever [13] and prosthetic valves have shown little or no evidence of infection in the valve ring (3 out of 5 patients had no vegetations found) [14].

The major clinical presentation was unexplained illness in a patient with known valvular disease [13]. The diagnosis can be delayed due to the protean manifestations of this entity and some patients have undergone several valve replacements before a diagnosis was made [13].

This patient was submitted to two surgical interventions of the mitral valve due to a mechanical valvular leak, one of which was assumed to be a consequence of a culture-negative endocarditis. Nine years later, he developed another dehiscence of the same valve with surgical indication and only at that time a Q fever serologic test was performed, leading to the diagnosis of Q fever endocarditis. We admit that this diagnosis was possibly delayed for all this time and *Coxiella burnetii* endocarditis of the mitral valve could have been present as early as 2006 with recurring infections of the replacement valves until the diagnosis was made serologically and therapy instituted. Wiener-Well Y. *et al.* described 9 patients with Q fever endocarditis during a 19-year period, three (33%) of which were unexpected and diagnosed after elective valve surgery [3].

Laboratory manifestations include anaemia, elevated erythrocyte sedimentation rate and polyclonal hypergammaglobulinemia. Leukocyte count may be normal, increased or decreased. Thrombocytopenia and elevated hepatic enzyme levels are

commonly found [8]. Autoantibodies are also frequent in chronic Q fever such as rheumatoid factor, anti- smooth muscle, antinuclear and antimitochondrial antibodies and also positive Coombs' test [15] but in this case all the autoimmune tests were negative.

The gold standard for the diagnosis of Q fever is indirect immunofluorescence (IF). Phase I antibodies are raised in chronic disease and IF titres IgG to phase I antigen of 1:800 or more is considered diagnostic for endocarditis [8]. Some authors say that PCR has low sensitivity in blood and high sensitivity in tissue samples [5], but there is evidence of high sensitivity and sensibility of PCR in specialized laboratories [8]. In our patient both serology and PCR in blood were positive. The recommended treatment for Q fever endocarditis is doxycycline (100 mg/bid) plus hydroxychloroquine (200 mg tid) until a target of $<$1:800 for IgG is achieved. Generally, a minimum of 18 months is needed [16].

According to Million et al. who published the largest cohort of Q fever endocarditis to date, for prosthetic valve infections, the optimum management includes a longer course of therapy (24 months) with doxycycline and hydroxychloroquine [17]. Intolerance to the recommended drugs, namely photosensitivity can be a problem, and regular heart and eye examinations are needed [16]. When untreated, the disease is usually fatal and, even with appropriate treatment, is associated with a mortality of 10% at five years [17]. Million et al. identified that *Coxiella burnetii* endocarditis on prosthetic valves (compared with the general population and with patients with other valvular heart diseases) was associated with higher mortality, more frequent stroke, delayed serological cure, need for longer treatment course and higher risk of relapse [17].

Our patient is still on treatment and free of disease after 8 months of doxycycline plus hydroxychloroquine.

Conclusion

We consider this case of a major importance to highlight the need to consider the diagnosis of chronic Q fever not only in the presence of a culture-negative endocarditis but also when unexplained valvular leaks occur in prosthetic valves. The authors recommend that all patients with negative blood culture endocarditis or unexplained dehiscence of prosthetic valves undergo serological testing for Q fever.

Ethical statement

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. The authors report no ethical disclosures.

Contributors

RF, FS, PA and JA were responsible for the patient's management during hospitalization and follow up after discharge, have collected all significant clinical information and drafted this manuscript.

JPT and MA were extremely important in collecting technical surgical data and also reviewed this paper. LS, ACC and AS have reviewed, redrafted and given significant contribution to the final version.

All authors have given final approval of this version.

Submission declaration and verification

The authors declare that the paper described has not been published previously.

Competing interests

The authors declare that they have no competing interests.

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