A case of recurrent fever in an older man caused by Coxiella burnetii

Title:

A case of recurrent fever in an older man caused by Coxiella burnetii.

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Abstract

Q fever is a zoonosis caused by the intracellular bacterium Coxiella burnetii. While it is mostly an asymptomatic infection, acute disease can manifest as fever associated with signs of pneumonia or hepatitis. Chronic Q fever develops in 1-5% of infected persons. Patients with a history of cardiac valve surgery, vascular prosthesis or vascular aneurysm; and to a lesser extent patients with pre-existing valvular disease, immune deficiencies or renal insufficiency are at highest risk. Most common manifestations are Q fever endocarditis and Q fever vascular infection. We present a case of chronic Q fever, followed by a summary of available literature.

Keywords:

Q Fever; Coxiella burnetii; Endocarditis; Zoonosis; Recurrent Fever

Introduction

Q fever is a zoonosis caused by the intracellular bacterium Coxiella burnetii. Cattle, sheep and goats are the primary reservoirs. The highest number of organisms is shed in birth products, but also in urine, milk and feces of infected animals. Humans are usually infected by aerosols, directly from birth fluids or through inhalation of contaminated dust.[(1)] Q fever is an endemic disease in certain regions of the world, such as the southeast of France, Spain and the Middle East. Sporadic cases can occur in virtually every country in the world, with the exception of New Zealand and Antarctica. Additionally, outbreaks have been described. An example is the recent outbreak in the Netherlands (2007-2010), involving more than 4000 human cases.[(1)] Symptomatic acute Q fever occurs in approximately half of infected persons after an incubation period of 2-3 weeks. It most often manifests as fever associated with signs of pneumonia or hepatitis. Chronic Q fever develops in 1-5% of infected persons.[(1)] Patients with a history of cardiac valve surgery, vascular prosthesis or vascular aneurysm; and to a lesser extent patients with pre-existing valvular disease, immune deficiencies or renal insufficiency are at highest risk.[(2)] Risk for chronic infection is also higher in pregnant women and in patients older than 60 years.[(2)] Most common manifestations are Q fever endocarditis and Q fever vascular infection. Less frequently reported manifestations are chronic infections during pregnancy, bone and joint infections.

We report a case of chronic Q fever endocarditis in an older man with recurrent fever and asthenia.

Case

After a two weeks observation for fever of unknown origin in a local hospital, an 85-

year-old man was referred to the university outpatient clinic of general internal medicine for further diagnostics. He complained of fever and clinical deterioration since 2 months. He had monthly an episode of high spiking fever with chills for a couple of days. He reported loss of strength, myalgia, intermittent vomiting, anorexia and night sweats. Medical history showed bio-prosthetic aortic valve replacement in 2012 due to aortic stenosis, mitral regurgitation, heart failure with preserved ejection fraction, chronic renal insufficiency and radical prostatectomy for prostate carcinoma. Chronic medication included nebivolol, aspirin, furosemide and simvastatin. Clinical examination showed hepatosplenomegaly, bilateral pulmonary crepitations and malleolar edema. Blood work showed normal leukocyte count, moderately elevated C-reactive protein level (79 mg/L) and erythrocyte sedimentation rate (75 mm/hr) and normocytic anemia. Blood and urine cultures were negative. Thorough anamnesis revealed frequent contact with sheep; he stopped farming himself but regularly helped at~~in~~ his son's farm. Serology for EBV, CMV, HIV, hepatitis A-B-C, Borrelia, Treponema and Brucella was negative for acute infection. Q-fever serology was not interpretable. Protein electrophoresis showed a monoclonal gammopathy IgG lambda. Auto-immune screening including ANA and ANCA was negative. Radiography and CT scan of the thorax showed mild interstitial changes in both lower lobes. CT scan of the abdomen was normal except for a slight splenomegaly. Transesophageal echocardiography (TEE) was performed twice and showed no vegetations. Bone marrow examination showed no abnormal hematopoiesis or malignant clone. ^{18}FDG-PET scintigraphy was performed and showed no FDG-avid lesions. Fever eventually resolved spontaneously and patient was discharged.

Three weeks later patient experienced a new episode of fever and a weight loss of 5 kg over the past 2 months was noted. Blood and urine cultures were repeatedly negative. Parasite blood smear as well as interferon gamma release assay for M. tuberculosis were negative. Auto-immune screening was repeated and showed an elevated rheumatoid factor (70 IU/ml). Bronchoscopy with bronchoalveolar lavage was refused by the patient. A new Q-fever serology showed very high phase I and phase II IgG (both titers >1:32768). Phase I and II IgM were 1:4096 and 1:2048 respectively. Diagnosis of probable chronic Q fever was made, as by the Dutch consensus guidelines (See Table 1 [1]). TEE was repeated and showed no vegetations. Since the presence of an aortic bio-prosthesis, the suspicion of Q fever endocarditis was high. Treatment with doxycycline 100 mg two times daily and hydroxychloroquine 200 mg three times daily was started. A favorable clinical response was noted with complete disappearance of febrile episodes. The activity level of the patient, which previously was very low, improved remarkably. C-reactive level has completely normalized. Currently, patient reports no side effects of therapy.

Discussion

Diagnosis in our patient was based on the presence of high titer Q fever phase I IgG in a patient with a prosthetic cardiac valve who presents with recurrent fever of unknown origin and non-specific constitutional symptoms (fatigue, weight loss, night sweats). Diagnosis of chronic Q fever is challenging. Since culture and PCR on serum or blood samples have low sensitivity (40-53% and 23% respectively), diagnosis relies mainly on serology.[1] Acute Q fever is characterized by a predominant antibody response to C. burnetii phase II antigen, whereas chronic infection is associated with persistently high phase I IgG titer (> 1:800 or 1:1024

depending on the type of immune fluorescence assay used).[1] The definition and diagnostic criteria of chronic Q fever are still a matter of debate. Different diagnostic criteria have been proposed by the Dutch Q fever Consensus group (table 1) [1] and by the French National Reference Center in Marseille (table 2) [3].

The patient we report oned is planned to be treated for Q fever prosthetic valve endocarditis, i.e. for a total treatment duration of at least 24 months [4], despite the absence of echocardiographic signs of endocarditis. In a retrospective study of the French National Referral Centre which included 103 patients with Q fever endocarditis, echocardiography showed a vegetation in only 28% of cases. A cardiac abscess was noted in only 7% and a prosthetic avulsion in 3%.[4] The most common abnormality found by echocardiography in this study was a new or worsening valvular insufficiency which occurred in 75% of patients.

^{18}F-FDG PET scintigraphy was performed in our patient but did not show enhanced uptake. Literature shows that ^{18}F-FDG PET/CT is a valuable tool for the localization of vascular Q fever infections. In a retrospective study of Barten et al. studying 52 chronic Q fever patients, ^{18}F-FDG PET/CT was positive in 10/13 (77%) of proven chronic Q fever cases. 7 patients had an infected aneurysm, the remaining 3 patients had an infected vascular prosthesis.[2] The value of ^{18}F-FDG PET/CT to detect Q fever endocarditis is less clear and further research is needed as the available evidence relies mainly on case reports. Notwithstanding this, It it is included as a major diagnostic criterion by Raoult D.[3]

In the presented case, no acute Q fever infection episode was identified. Analysis of the Dutch National Chronic Q Fever Database, which includes 284 cases of chronic Q fever, showed that a known acute Q fever episode was present in only 38% of patients.[5] Moreover, a large retrospective study including 103 Q fever endocarditis

patients showed that an acute Q fever episode was recalled in only 16% of patients.[4]

Treatment of chronic Q fever endocarditis consists of doxycycline 100 mg twice daily and hydroxychloroquine 200 mg three times daily. Prolonged treatment is necessary due to the intracellular location of C. burnetii, making it difficult to eradicate. Doxycycline treatment duration of less than 18 months is an independent risk factor for serological relapse (HR 9.69; 95% CI 1.08-86.7).[4] Duration of therapy should therefore comprise at least 18 months. In patients with prosthetic valves, the optimum treatment duration is 24 months, since patients treated for less than 24 months showed more relapse.[4] Because of the long treatment duration, patients should be motivated and possible side effects should be explained. Hydroxychloroquine has retinal toxicity, consequently a baseline ophthalmic examination should be performed before treatment and every six months thereafter. Both doxycycline and hydroxychloroquine can cause photosensitivity.

Serological monitoring is warranted during the treatment. In the retrospective study of Dutch chronic Q fever patients, patients were considered to be cured if the IgG phase I titer showed at least a fourfold decrease or had declined to <1:1024 during serological follow-up.[2] Serological follow-up is also of prognostic importance because absence of a four times decrease of phase I IgG at 1 year (HR 5.69; 95% CI 1.00-32.22) and the presence of phase II IgM at 1 year (HR 12.08; 95% CI 3.11-46.8) also proved to be independent mortality risk factors.[4] ~~After~~Once therapy is ended ~~end of treatment,~~ serological follow-up for at least 5 years is necessary since serological relapse is described (risk is 10% at 5 years).[4] Independent factors related to serological relapse are a doxycycline treatment duration of less than 18 months, as described earlier, and endocarditis on a prosthetic valve (HR 21.3; 95%

CI 2.05-221.8).[4]

Without therapy prognosis is bad, with a mortality rate of up to 60%.[4] Even in treated patients, chronic Q fever is a severe infection ~~which carries~~having a high mortality rate. In the Dutch National Chronic Q fever database, death attributable to the complications of chronic Q fever occurred in 13.0% of all patients with proven or probable chronic Q fever.[5] Vascular infection carries the highest mortality rate (18.0%), followed by endocarditis (9.3%).[5] This result is comparable to the retrospective study published by Million et al., describing 71 patients with Q fever endocarditis who were followed during 5 years.[4] In this group, endocarditis-related mortality was 10%. Age is an independent predictor of mortality (hazard ratio 1.59 per 10-year increase of age; 95% CI 1.14-2.21) [5], as well as endocarditis on a prosthetic valve (HR 6.04; 95% CI 1.47-24.8) [4].

Conclusion

Q fever endocarditis due to chronic Q fever infection is a disease associated with significant morbidity and mortality, which is difficult to diagnose because of the absence of major diagnostic criteria in the majority of patients. High clinical suspicion is needed, especially in endemic areas, or when contact with farm animals is described. Treatment consists of doxycycline and hydroxychloroquine for a total duration of 18-24 months.

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Table 1 Diagnostic criteria of chronic Q fever

Dutch consensus guideline on chronic Q fever diagnostics (1)

A. Proven chronic Q fever

1. Positive C. burnetii PCR in blood or tissue OR

2. IFA ≥1:1024 for C. burnetii phase I IgG AND

- definite endocarditis according to the modified Duke criteria OR

- proven large vessel or prosthetic infection by imaging studies (^{18}FDG-PET, CT, MRI or AUS)

B. Probable chronic Q fever

IFA ≥ 1:1024 for C. burnetii phase I IgG AND one or more of following criteria:

- Valvulopathy not meeting the major criteria of the modified Duke criteria

- Known aneurysm and/or vascular or cardiac valve prosthesis without signs of infection by means of TEE/TTE, ^{18}FDG-PET, CT, MRI or abdominal Doppler ultrasound

- Suspected osteomyelitis or hepatitis as manifestation of chronic Q fever

- Pregnancy

- Symptoms and signs of chronic infection, such as fever, weight loss and night sweats, hepatosplenomegaly, persistent raised ESR and CRP

- Immunocompromised state

C. Possible chronic Q fever

IFA ≥ 1:1024 for C. burnetii phase I without manifestations meeting the criteria for proven or probable chronic Q fever

Definition of Q fever endocarditis - French National Reference Center (3)

A. Definite criterion

Positive culture, PCR, or immunochemistry of a cardiac valve

B. Major criteria

Microbiology: positive culture or PCR of the blood or an emboli or serology with IgG I antibodies ≥ 1:6400

Evidence of endocardial involvement: echocardiogram positive for IE: oscillating intra-cardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or abscess; or new partial dehiscence of prosthetic valve; or new valvular regurgitation (worsening or changing of pre-existing murmur not sufficient).

PETet-scan showing a specific valve fixation and mycotic aneurism.

C. Minor criteria

Predisposing heart condition (known or found on echography)

Fever, temperature > 38°C

Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurism, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions.

Immunologic phenomena: glomerulonephritis, Osler's nodes, Roths spots, or rheumatoid factor.

Serological evidence: IgGI antibodies ≥ 1:800 < 1:6400

Diagnosis definite

1) 1A criterion
2) 2B criteria
3) 1B criterion, and 3C criteria (including 1 microbiology evidence, and cardiac predisposition)

Diagnosis possible

1) 1B criterion, 2C criteria (including 1 microbiology evidence, and cardiac predisposition)
2) 3C criteria (including positive serology, and cardiac predisposition)