Endocardite à Coxiella burnetii compliquée d'une ostéoarthrite des genoux

Bilateral knee osteoarthritis and infectious endocarditis caused by Coxiella Burnetii: a case report

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Résumé

Il s'agit du cas d'une femme âgée de 46 ans chez qui le diagnostic d'une endocardite infectieuse à Coxiella burnetti sur valve prothétique et à culture négative a été établi. L'échocardiographie transthoracique et transoesophagienne n'ont révélé ni végétation ni déhiscence partielle de la prothèse. Malgré un traitement efficace par doxycycline et hydroxychloroquine, notre patiente a développé une arthrite avec ostéonécrose bilatérale des deux genoux. Des biopsies osseuses et synoviales ont été alors pratiquées. La recherche de Coxiella burnetii par polymerase chain reaction (PCR) était positive dans la biopsie de la synoviale. Les antibiotiques ont été poursuivis pendant 42 mois avec une amélioration clinique et sérologique.

Mots-clés

Fièvre Q, endocardite, ostéoarthrite bilatérale

Summary

This is a case of a 46 year old woman in which the diagnosis of a culture-negative prosthetic valve endocarditis caused by Coxiella burnetti has been established. The transthoracic and transesophageal echocardiography did not reveal any vegetation or new partial dehiscence. Despite effective treatment by Doxycycline and Hydroxychloroquine, our patient has developed bilateral arthritis and osteonecrosis of both knees. Synovial and bone biopsies were then sampled. Coxiella burnetii polymerase chain reaction (PCR) was positive for the synovial one. Antibiotics were continued for 42 months with clinical and serological improvement.

Keywords

Q fever, endocarditis, bilateral osteoarthritis

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INTRODUCTION

Q fever is a worldwide zoonosis caused by an intracellular bacterium: *Coxiella burnetii* (*C. burnetti*) and can be presented as either acute or persistent disease. Culture negative endocarditis and infections of aneurysms or vascular prostheses are the most common manifestations of these persistent infections. Arthritis, osteomyelitis and hepatitis are less frequent. We report the observation of a patient having both endocarditis and osteoarticular infection.

CASE REPORT

A forty six-year-old female patient was presented to our clinic complaining from prolonged fever, polyarthralgia and dry cough since 8 months with no history of night sweats, cutaneous or neurological symptoms.

Her medical history includes a mitral valve replacement with a prosthetic heart valve on 1996 and complete arrhythmia treated by amiodarone and acenocoumarol.

She had habits of raw-milk consumption and has a close contact with domestic animals, mainly sheep and goats.

The physical examination has revealed fever up to 38,3°C and irregular heartbeats. The patient's lungs were clear on auscultation and a mild splenomegaly was noticed.

The biological analyses have shown the following anomalies: hight erythrocyte sedimentation up to 35 mm/Hr and C-reactive protein up to 34,5 mg/l.

Further analyses have revealed liver enzyme abnormalities with an alanine aminotransferase concentration of 100 U/L while the alkaline phosphatase concentration was within the average. The Gamma-Glutamyl Transferase (GGT) rate was 87 UI/l and the phosphatases alcalines (PAL) one was 551 UI/l. The rheumatoid factor was positive.

The transthoracic and transesophageal echocardiography showed a dilated left atrium but did not reveal any vegetation or new partial dehiscence. In the meantime, three sets of blood cultures were performed.

Given the suspicion of an infective endocarditis, and as the blood culture result were negative, serologies for *Brucella* species and *Legionella* species were performed and they were negative. Nevertheless, the results of serological tests for *C. burnetti* were positive, with phase I antigen titer of 1/6400 and phase II titer of 1/12800 which is consistent with the diagnosis of chronic Q fever.

Our patient was diagnosed with *C. burnetti* endocarditis with reference to Ducke criteria (table 1 and 2): In fact, our patient has one major criterion (phase I antigen titer > 1:800) and three minor criteria (predisposing heart condition, fever over 38 and positive rheumatoid factor).

She was treated by Doxycycline 200 mg/day and Hydroxychloroquine 200 mg three times per day. The patient had poor adherence treatment.

Table 1: Definition of infective endocarditis (IE) according to the modified Duke criteria

Definite IE
Pathological criteria
- Microorganisms demonstrated by culture or on histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
- Pathological lesions; vegetation or intracardiac abscess by histological examination showing active endocarditis

Clinical criteria
- 2 major criteria; or
- 1 major criterion and 3 minor criteria; or
- 5 minor criteria

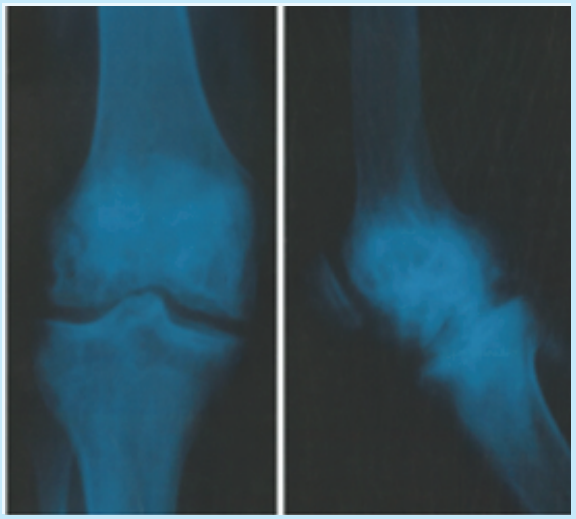
Possible IE
- 1 major criterion and 1 minor criterion; or
- 3 minor criteria

Rejected IE
- Firm alternate diagnosis; or
- Resolution of symptoms suggesting IE with antibiotic therapy for ≤4 days; or
- No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or
- Does not meet criteria for possible IE, as above

Table 2: Definitions of the terms used in the definition of infective endocarditis according to the modified Duke criteria

Major criteria
1. Blood cultures positive for IE
a. Typical microorganisms consistent with IE from 2 separate blood cultures:
• Viridans streptococci, Streptococcus gallolyticus (Streptococcus bovis), HACEK group, Staphylococcus aureus; or
• Community-acquired enterococci, in the absence of a primary focus; or
b. Microorganisms consistent with IE from persistently positive blood cultures:
• ≥2 positive blood cultures of blood samples drawn >12 h apart; or
• All of 3 or a majority of ≥4 separate cultures of blood (with and last samples drawn ≥1 h apart); or
c. Single positive blood culture for Coxiella burnetii or phase I IgG antibody titre >1:800
2. Imaging positive for IE
a. Echocardiogram positive for IE:
• Vegetation;
• Abscess, pseudoaneurysm, intracardiac fistula
• Valvular perforation or aneurysm;
• New partial dehiscence of prosthetic valve.
b. Abnormal activity around the site of prosthetic valve implantation detected by 18F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT.
c. Definite paravalvular lesions by cardiac CT.
Minor criteria
1. Predisposition such as predisposing heart condition, or injection drug use.
2. Fever as temperature >38°C.
3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions.
4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.

Five months after treatment start, our patient complained from pain and left knee swelling. Physical examination showed a warm, swollen and painful joint. Knee X-rays prove a joint damage and geodes (figure 1).



(a) (b)

Figure 1: Antero-posterior (a) and lateral (b) view radiograph showing lytic lesions and a geodes in the left knee

Computed Tomography (CT) presents effusions, joint inflammation and left knee osteonecrosis with reactive synovitis. The synovial fluid contained a low white blood cells count with a high rate of proteins (42 g/l). Its culture was negative. At this time, serology for *C. burnetti* remains unchanged. The patient had an arthrotomy of the knee with drainage. The bacteriological specimen had a negative culture result as well as *Mycobacterium* search. Synovial and bone biopsies were then sampled. Given the context of a *C. burnetti* endocarditis, we performed a polymerase chain reaction (PCR) to detect this bacterium on bone and synovial biopsies. The result was positive on the synovial one. A CT control was performed and showed bilateral knee osteoarthritis.

After 12 months of treatment, the patient showed signs of clinical improvement. The fever and joint pain had disappeared. The inflammatory syndrome regressed and the hepatic cytolysis improved. The phase I antigen titer decreased to 1/800 at the 23th month of treatment then increased to 1/1600 eight months later. The patient presented a serologic failure due to poor treatment adherence. Hydroxychloroquine treatment was stopped after 32 months due to its toxicity anomalies as showed in the electroretinography.

The phase I antigen titer decreased to 1/400 after 42 months of treatment; therefore we have decided to stop the treatment.

DISCUSSION

C. burnetii has been reported worldwide, mainly in Mediterranean countries, especially France and Spain where the situation is endemic (1). The main reservoirs are cattle, sheep and goats. Recently, birds, domestic mammals, marine mammals, ticks and reptiles have been reported to shed the bacterium (2). *C. burnetii* is mostly found in birth products, but can also be found in urine, feces and milk of infected animals (3,4). Due to its high resistance in the environment, humans are most often infected by inhalation of aerosols produced in contaminated locations. Transmission can occasionally be done through percutaneous exposure, digestive tract or sexual intercourse (1, 2).

In humans, primary infection can be asymptomatic; it is nearly symptomatic in only less than half of cases. The host immune response is almost sufficient to control *C. burnetii* infection (5). By contrast, the ability to evade the immune response is known and depends on host factors, especially immunosuppression (6,7).

C. burnetii persistent infections can be fatal if not diagnosed, especially endocarditis and vascular infection. The early detection of these infections was considered as a public health problem (3). Almost all patients with acute Q fever evolving into endocarditis had cardiac lesions, with the rare exceptions of immunocompromised patients mainly those having cancer (8). The major predisposing factors are valvular prostheses, history of rheumatic fever and moderate mitral insufficiency. However, other important factors are often not clinically diagnosed, as mitral valve prolapsus and aortic bicuspidy (9,10). The lack of vegetation is usual in echocardiography. It occurs in almost two third of cases (10). Another mechanism different from the colonization of cardiac valves is possible. This suggests that the immune context can be involved (11,12), especially that *C. burnetti* infection is initially associated with high levels of anticardiolipin antibodies (13). In relation with vascular infections, preexisting aneurysms or vascular grafts are the major predisposing factors which are associated to elevated mortality rates up to 25% (14). Osteoarticular infections represent 1 to 2% of *C. burnetii* clinical manifestations (6,15). They are an emerging clinical entity for which functional outcome depends on early and adequate treatment (16). Prosthesis may be a predisposing factor, moreover further studies need to confirm this (17). In the last decade, more case reports of bone and joint *C. burnetti* infections are reported (3). Osteomyelitis, often multifocal, appears to be a usual presentation in children. For adults, the clinical presentation is more variable. Isolated osteomyelitis, spondylodiscitis, arthritis, tenosynovitis, coxitis, sacroiliitis and bursitis are the forms mentioned in the literature (3). These cases should be confirmed by PCR or culturing of the

lesion (10). Using an 18 F-FDG PET/CT can be useful for the diagnosis of *C. burnetii* osteoarticular infections and allowed then to establish diagnostic criteria for this type of infection (16–18). Other manifestations of persistent infections include also persistent lymphadenitis and hepatitis (18).

In general, persistent Q fever is associated with elevated phase I IgG titers. An increase in the level of these antibodies is correlated with higher positive predictive values (PPV) for the diagnosis of endocarditis: the threshold of ≥800 is usually described and the PPV reached 75% for IgG I titers ≥1/6400 (19). Therefore, persistent high levels of phase I antibodies 6 months after finishing the treatment should be alarming and investigation for persistent infection should be performed.

The relevance of PCR-based testing in the diagnosis is debatable, as PCR result can be positive in apparently healthy patients (12) and can be negative in case of endocarditis with very high antibody levels (20).

Doxycycline (200 mg/day) presents the reference treatment of *C. burnetti* infections. In case of endocarditis, a combination with hydroxychloroquine (200 mg 3 times/day) is necessary, this antibiotic raise the pH in the pseudolysosomal vacuole to restore doxycycline activity. In addition, this association has shown bactericidal activity in vitro (3). In the literature, the most common side effects are photosensitization (23%), digestive intolerance (7%) and ocular toxicity (4%) (21). Endocarditis-related death rate is on average 4% after 3 years of follow-up and mortality independent factors are age at diagnosis, prosthetic valve and no decrease of a 4-fold in IgG and IgA at 1 year of follow-up (21). The duration of treatment for patients with native valve endocarditis is 18 months and is 24 months for those with prosthetic valve. In the case of no decrease of a 4-fold in IgG and IgA and no disappearance of IgM II, the treatment can be continued for longer period like as the case in our observation (3).

The continuous monitoring process involves a combination of clinical examination and serologies to be performed every 3 months during treatment. Otherwise, we propose continuing longer serological monitoring, until 5 years of follow-up. In fact, serological relapse was found in 6% of patients at 5 years of follow-up (21).

Nowadays, the prevention of *C. burnetti* infection is a primary target. It consists primarily of avoiding the production and inhalation of contaminated dust and the consumption of potentially contaminated food.

CONCLUSION

The diagnosis of *C. burnetti* persistent infections may be difficult and delayed. Serology is not sufficient to identify the type of this infection. The search for deep or multiple infectious sites should be systematic.

The better comprehension of susceptibility factors leading to persistent infection could allow better management of these severe infections. Finding new more effective and less toxic treatment and other combinations is highly required and would be the subject of future research.

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