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Case report

A zoonotic cause of blood culture-negative infective endocarditis in Belgium: Case report and review of the literature on Q fever

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ABSTRACT

Q fever is a worldwide zoonotic infection caused by *Coxiella burnetii*. In Belgium, the disease must be notified, and the incidence is low. Human contamination is mostly due to sheep and goats. Herein, we report a case of chronic Q fever presenting as a prolonged fever in a patient with a history of valve prosthesis. Blood culture-negative endocarditis was diagnosed through an assessment including echocardiography and systematic serological testing. Despite the absence of travel abroad or obvious contact with domestic or wildlife animals, *C. burnetii* phase I and phase II IgG antibody titers were > 1:8192, and polymerase chain reaction performed on blood was positive for *C. burnetii*. Genotypic single nucleotide polymorphism (SNP) analysis of the pathogen strain identified a SNP-type 1 genomic group, which is associated with small ruminants in Belgium. The epidemiological investigation did not confirm the presence of positive *C. burnetii* cattle or sheep herds in the vicinity of the patient's workplace and home, nor in the pest animals surrounding the workplace. Patients with risk factors for chronic Q fever should be tested for *C. burnetii* infection in case of prolonged fever of unknown origin, osteomyelitis, abscess or blood culture-negative endocarditis, even in the absence of direct exposure to animals.

Introduction

Infective endocarditis (IE) should be suspected when a patient with a history of valve abnormalities presents with a prolonged fever of unknown origin. If the cardiac ultrasound shows signs of IE, the microbiological diagnosis depends primarily on the positivity of blood cultures. When negative, the 2015 guidelines of the European Society of Cardiology [1] recommend to perform a systematic serological testing, according to the local epidemiology. Although the incidence of Q fever is low in Belgium, we report a case of blood culture-negative endocarditis due to *Coxiella burnetii* in a patient with a history of pulmonary and aortic valve repair, and no obvious direct exposure to animals.

Case presentation

A 43-years old patient, with a history of congenital stenotic bicuspid aortic valve, had underwent two surgeries: he had a Ross procedure in 1998, and three years later a reintervention for aortic valve replacement by mechanical prosthesis and replacement of the pulmonary homograft. Medication consisted in acenocoumarol, bisoprolol and esomeprazole. The latest annual transthoracic echocardiography (TTE) in July 2020 showed no sign of significant valvular regurgitation or stenosis. In September 2020, the patient consulted his general practitioner about a sudden onset of daily fever (≥ 38 °C), myalgia, mild headache and arthralgia (knees, wrists and fingers). He described a 24 h-duration erythematous and pruritic maculo-papular rash, localized on the trunk and limbs. He was involuntarily losing weight, complained of cognitive fog and of shortness of breath on moderate to mild exertion. He had no

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recent history of tropical travel or insect bite, was not in close contact with either domestic or farm animals, and had no sexual or drug behavioral risk. Initial laboratory tests showed a mild inflammatory syndrome (CRP 18.4 mg/L), microcytic anemia (Hb 11.9 g/dL) and thrombocytopenia (platelet count $102.10^3/\mu L$). Although lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) were abnormal (respectively 477 IU/L, 51 IU/L and 158 IU/L), transaminase levels and total bilirubin were within the normal range. HIV, hepatitis A, B and C, *Cytomegalovirus* and *Mycoplasma pneumoniae* serologies were negative. A TTE in October 2020 showed no change of valve function or aspect. A chest computed tomography (CT) scan was normal in December except for two small ground-glass lung infiltrates. An abdominal ultrasound in January 2021 was normal. Tuberculin test was negative and SARS-CoV-2 polymerase chain reaction test on nasopharyngeal swab was repeatedly negative in 5 months. The patient was treated by several short courses (7–10 days) of antibiotics during that period (doxycycline, amoxicillin-clavulanic acid, clarithromycin, ciprofloxacin). Although there was a transient improvement on doxycycline and clarithromycin, none of them resolved the clinical picture. In February 2021, a third TTE showed a vegetation on the pulmonary valve that was confirmed by transoesophageal echocardiography (TOE). The vegetation measured 8/4.4 mm (Fig. 1). There was no abscess or abnormality on the other valves, including the mechanical aortic valve. Clinical examination revealed a heart murmur (2/6) at the pulmonary valve site, banal aortic implant noise, no sign of septic embolus, an hepatosplenomegaly and a body temperature at 38.1 °C. Ciprofloxacin was stopped. Blood cultures were drawn repeatedly and were negative. Auto-immune assessment was negative except for an increased rheumatoid factor (67 IU/mL). Blood test showed persistant microcytic anemia (Hb 10.7 g/dL), mild inflammatory syndrome (CRP 15 mg/L) and slightly increased ALP (189 IU/L) and GGT (82 IU/mL). The following serologies were negative: *Legionella pneumophila*, *Brucella* spp, *Bartonella* spp, *Mycoplasma pneumoniae*, and *Aspergillus* spp. *Coxiella burnetii* phase II IgG screening test was measured $>$ 1:400, hence a sample was sent to a reference laboratory: phase II and phase I IgG were $>$ 1:8192, compatible with a diagnosis of chronic Q fever, herein the form of endocarditis. *C. burnetii* was also detected by PCR on blood. Genotypic single nucleotide polymorphism (SNP) analysis identified the C. *burnetii* strain as of the SNP-type 1, which is associated with small ruminants such as sheep and goats in Belgium. Cardiac positron emission tomography (PET) scan showed the accumulation of radiolabelled white blood cells on the pulmonary valve only. No sign of distant infection focus was demonstrated. Patient was started on doxycycline 100 mg bid and hydroxychloroquine 200 mg tid for 18–24 months, and showed slow but definite improvement of his symptoms within the 6 months of ongoing follow-up. Transthoracic echocardiography showed the near disappearance of the cardiac mass within the same time interval.

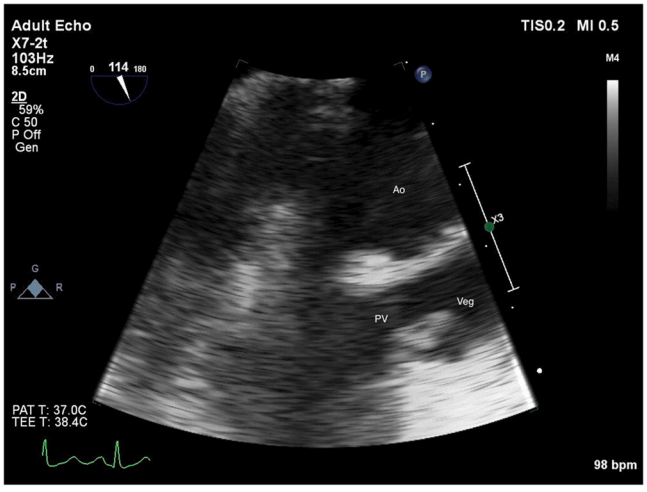

Fig. 1. Vegetation on the pulmonary homograft on the transoesophageal echocardiography. Ao: aorta, PV: pulmonary valve, Veg: vegetation.

Discussion

Coxiella burnetii is an obligate intracellular Gram-negative coccobacillus belonging to the *Coxiellaceae* family. It is the causative agent of Q fever, a worldwide zoonosis. Contaminated vaginal secretions, feces, birth products and milk of a broad animal host range, predominantly sheep, cattle and goats [2], contain small bacterial spore-like particles that are shed into the barnyard dust. Wind dispersal occurs mostly within a 5–10 km radius and the main source of transmission is airborne [3]. Therefore, if certain professions (e.g. farmers, veterinarians, slaughterhouse workers) or activities (e.g. hunters) are strong risk factors due to exposure to domestic or wild animals, direct contact with animals is not necessary to develop acute Q fever [4].

Q fever is a notifiable disease in Belgium. In 2018, 18 cases were reported to the Belgian Institute of Health, among which a third were confirmed cases. In 2019, *C. burnetii* serological incidence was $1/10^6$ inhabitants, probably underestimated due to the absence of symptoms or their lack of specificity. Indeed, after a median incubation period of 18 days [5], acute Q fever appears symptomatic in only 40 % of patients, mainly presenting with flu-like symptoms (fever, fatigue, dry cough, retrobulbar headache). Anorexia, sweats and weight loss might also occur. Atypical pneumonia or hepatitis are less common presentations (2 %). Skin eruption and gastro-intestinal symptoms are more common in children. Liver enzymes can be elevated. Serology by indirect immunofluorescence assay is the diagnostic gold standard. Detection of *C. burnetii* deoxyribonucleic acid (DNA) by PCR in a clinical specimen may also confirm the diagnosis. Spontaneous resolution is frequent, however antibiotherapy reduces the duration of symptoms and the likelihood of chronic Q fever. Risks factors for chronic Q fever include heart valve defect or implant, blood vessels abnormalities such as aneurysms or grafts, defective T-cell mediated immunity and pregnancy [6]. Serological monitoring at 3 and 6 months is recommended for any patient diagnosed with acute Q fever, and should be extended to a minimum period of two years in patients with risk factors for chronic *C. burnetii* infection.

Chronic Q fever develop among 0.5–2 % patients with acute Q fever. Endocarditis is the most frequent form of chronic Q fever (60–70 % of all cases), followed by infection of aneurysms and vascular prostheses [7]. The systematic diagnostic approach in a patient with a prolonged fever and risk factors for IE requires to perform echocardiography and blood cultures. Negative blood cultures can occur in up to 31 % of all cases of IE [1]. It commonly arises as a consequence of previous antibiotic administration. Blood culture-negative endocarditis newly recognized by TTE should be confirmed by TOE, and serologies including *Coxiella burnetii*, *Bartonella* spp, *Legionella pneumophila*, *Brucella* spp, *Mycoplasma pneumonia*, and *Aspergillus* spp should be proposed.

In this case, the low incidence of Q fever in Belgium, the difficult access to blood cultures in outpatient settings, and the repetitive use of empirical antibiotics without definitive diagnosis have certainly contributed to the late diagnosis. The samples collected in livestock and pest animals in the vicinity of the patient's workplace and home as part of the epidemiological investigation, were negative for *C. burnetii* according to the serological and PCR analyses. The *C. burnetii* infection in animals, named coxiellosis, is widespread in all Belgian domestic ruminants. The human contamination in Belgium is mostly linked to specific genomic groups such as SNP1 (as in our patient) and SNP6, which are mostly found in small ruminants [8].

The association of a definite IE (proved by two major criteria from the modified Duke classification) and *C. burnetii* phase I IgG titers well above the threshold of $\geq$ 1:1024, were conclusive for the diagnosis of chronic Q fever infection.

Other presentations of chronic Q fever include osteomyelitis and abscess, which commonest symptoms include fatigue (17–30 %) and pain (54.5 %). Pain is significantly more often present in osteomyelitis (RR 4.13, 95 % CI: 3,36–5,07), abscess (RR 3,59, 95 % CI: 3,28–3,93) and vascular infection (RR 2,46, 95 % CI: 1,99–3,03), compared to endocarditis [7]. A positive serology associated with a chronic focal pain should prompt the clinician to perform a magnetic resonance imaging (MRI) centered on the painful region. Fluorodeoxyglucose F18 (18-FDG) PET scan looking for distant foci or endocarditis may be part of the severity assessment.

Given the severe morbidity and mortality (100 % if untreated) associated with endocarditis [9], a prompt, targeted, and prolonged antibiotherapy, with or without surgery, is crucial and has been shown to increase survival (3-year mortality rate of 7 % when treated) [10]. Treatment pillar is doxycycline 200 mg/day in both acute and chronic Q fever infections, the first being treated for 14 days, and the second for $\geq$ 18 months in association with hydroxychloroquine 600 mg/day, in order to facilitate the bactericidal effect by phagolysosome alkalinization. Ophthalmological assessment should be planned at least once a year to exclude retinal toxicity, and more often if hydroxychloroquine daily dose exceeds 6.5 mg/kg of ideal body weight. Sun protection is mandatory to limit the risk of increased photosensitivity. Monthly serologic testing and clinical evaluation should be performed to assess decrease of *C. burnetii* phase I IgG and recovery of clinical symptoms during treatment. Favorable prognostic indicators at the end of the treatment of *C. burnetii* endocarditis are either a phase I IgG $\leq$ 1:800, or a fourfold decrease in phase I IgG and IgA and disappearance of phase II IgM [11]. A doxycycline serum concentration of at least 5 μg/mL was correlated with a $>$ 2-fold decrease in *C. burnetii* phase I antibody titers at one year in patients treated for a *C. burnetii* endocarditis [12]. Twice yearly serological monitoring of treated patients should continue for a minimum of five years after treatment.

In conclusion, Q fever is most likely an underestimated disease which can be responsible for outbreaks in Europe. Patients at risk for chronic Q fever should be promptly tested for *C. burnetii* infection in case of prolonged fever of unknown origin, atypical pneumonia, hepatitis, or blood culture negative endocarditis, even if there is no obvious contact with animals. Definite diagnosis is based on epidemiology, serology, PCR, TOE, PET scan and/or MRI. The treatment of chronic Q fever is challenging but significantly improves the survival.

CRediT authorship contribution statement

Van Noten Héloïse: Writing – original draft. **Mori M., Morissens M., Maillart E., Leemans S., Gvinda D., Channan EM, Clevenbergh P.:** Writing – review & editing.

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Ethical approval

A case report is a medical/educational activity that does not meet the definition of “research”, which is: "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." Therefore, the activity does not have to be reviewed by ethics committee.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying image. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Declaration of Competing Interest

The authors report no declarations of interest.

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