International Journal of Infectious Diseases 87 (2019) 166–169

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Case Report

A rare case of Prosthetic Joint Infection associated with *Coxiella burnetii*

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ARTICLE INFO

Article history:
Received 29 May 2019
Received in revised form 24 July 2019
Accepted 24 July 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Prosthetic Joint Infection
Coxiella burnetii
PCR
16s rDNA sequencing
Persistent infection

ABSTRACT

We report here the case of a Prosthetic Joint Infection (PJI) associated with *Coxiella burnetii* in a 62-year-old man with a revised total hip arthroplasty. The diagnosis was performed first by 16S rDNA sequencing on hip fluid aspirate, and confirmed by specific qPCR. Q fever has been reported in few cases of Prosthetic Joint Infections, often associated with chronic evolution and iterative surgeries. This case report alerts about such an unexpected diagnosis in a patient with no known risk factors.

Introduction

Coxiella burnetii is a Gram-negative obligate intracellular bacterium, responsible for Q fever (Eldin et al., 2017). This ubiquitous zoonosis affects mainly animal workers, goats and sheep, the two latter being major reservoirs. Several clinical entities of Q fever can be identified. It is commonly acknowledged that 60% of cases are asymptomatic (Bacci et al., 2012). In symptomatic cases, after a 2–3 week period of incubation, primary infection can be associated with a flu-like syndrome with fever, headaches and myalgia, or more severe symptoms such as pneumonia or hepatitis (Eldin et al., 2017). Some persistent focalized infections are also reported, such as endocarditis or endovascular infections (Eldin et al., 2017). Osteoarticular infections are also described, but considered as uncommon since they represent only 2% of Q fever cases identified in France according to a 14-year serologic study (Eldin et al., 2017; Raoult et al., 2000). Osteomyelitis is the most frequent form of osteoarticular infections (Bayard et al., 2015; Nourse et al., 2004), but spondylodiscitis, paravertebral abscesses and tenosynovitis have also been reported (Eldin et al., 2016). Prosthetic Joint Infections (PJIs) are increasingly described in the literature (Meriglier et al., 2018; Million et al., 2014; Tande et al., 2013). Indeed, osteoarticular infections and more specifically PJIs associated with *C. burnetii* could have been underdiagnosed in the past, because of the long evolution of the osteoarticular infection with low inflammatory signs and of the negative results of conventional culture (Angelakis et al., 2014). The use of molecular techniques, which allows diagnoses of Q fever PJIs even in unexpected contexts, alerts about such an emerging infection. Here, we report the case of a left-hip PJI associated with *C. burnetii*, in a context of multiple revised total hip arthroplasty (THA).

Case report

A 62-year-old-man presented to our Hospital for left hip pain and swelling, over a previously multirevised left THA in a context of hip dysplasia (three revisions of the hip prosthesis and five

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https://doi.org/10.1016/j.ijid.2019.07.028

reductions of dislocations). He also underwent a right THA in 2014, for the same pathology, and a right total knee arthroplasty for osteoarthritis 2 months before. This patient had a previous history of addictions to intra-venous drugs, alcohol and tobacco. On admission, no fever was noticed. Biological results indicated a raised C-reactive protein (68 mg/L) and a normal peripheral leukocyte count (8.01×10^9/L). Six peripheral blood cultures (BACT/ALERT®, bioMérieux, Marcy l'Etoile, France) remained sterile after 5 days of incubation. Standard-X ray showed an important cotyloidal and femoral destruction. A computed tomography scan was performed, but numerous artefacts due to the orthopedic implant complicated the interpretation of images. No probabilistic antimicrobial therapy was dispensed. The day following the admission, the patient underwent a fluid aspiration from the left hip under radioscopic guidance, which yielded a purulent fluid facing the greater trochanter. The aspirate was sent for bacteriological analysis. The standard bacteriological cultures, achieved on sheep blood agar (COLS+, Oxoid, Dardilly, France) in aerobic and anaerobic atmospheres, on chocolate agar (CHOCV, Oxoid) in air atmosphere with 5% CO_2, on Schaedler and Brain-Heart enrichment broths (bioMérieux) and in aerobic and anaerobic bottles (BACT/ALERT®), remained sterile after 7 days of incubation. Considering this culture-negative PJI diagnosis, 16S rDNA sequencing was achieved directly on the left hip fluid sample, as described previously (Weisburg et al., 1991). BLAST analysis of the sequence through the National Center for Biotechnology Information (NCBI) server (http://blast.ncbi.nlm.nih.gov) revealed a similarity of 100% with the 16S rDNA sequence of *C. burnetii* (GenBank accession NR_104916.1), with an overlap identity of 861/861 bp. This result was confirmed with a *C. burnetii*-specific real-time PCR conducted by the French National Reference Centre for Q fever (Institut Hospitalo-Universitaire Méditerranée Infection, Marseille, France) (Eldin et al., 2017). Additionally, positive Q fever serology was also observed, with phase I IgG $\geq$ 1:2048, phase II IgG $\geq$ 1:2048, phase I IgM of 1:512 and phase II IgM of 1:64. The serological profile with strongly positive phase I IgG serology was also in favor of persistent focalized infection (Eldin et al., 2017). A treatment with doxycycline (100 mg twice a day) and hydroxychloroquine (200 mg three times a day) was initiated for a length of 2 years. The two-stage surgical exchange of the left hip prosthesis has been delayed after several weeks of treatment. Three months after the initiation of the treatment, the patient had improved, with a significant decrease of hip pain.

Discussion

We report here a *C. burnetii* PJI, in a situation of multiple revised THA. Q fever is a zoonotic infection, in which osteoarticular symptoms are an uncommon presentation (Eldin et al., 2017). No risk factor for Q fever such as animal exposure was known for this patient, supporting the fact that this infection can be diagnosed in unexpected contexts. Few cases of such infection have been described in the literature, mostly occurring on previously revised arthroplasty (Meriglier et al., 2018; Million et al., 2014; Tande et al., 2013). In these cases, as reported here, clinical symptoms were often non-specific. Furthermore, the biological diagnosis remained difficult and this pathogen may have been under-recognized in periprosthetic osteoarticular samples. All these features suggest that *C. burnetii* could be considered as a potential PJI pathogen, especially in a culture-negative context.

Some epidemiological discrepancies in Q fever diffusion can be noticed between countries. Indeed, some endemic or outbreak situations can be observed. In endemic areas, sporadic cases are associated with high-risk activities. Large scale outbreaks can also occur, such as the one reported in the Netherlands between 2007 and 2010 (Delsing and Bleeker-Rovers, 2010). France is considered an endemic area concerning Q fever, even if localized outbreaks and hyperendemic foci have been described (Eldin et al., 2017). The leading reservoirs of *C.burnetii* are cattle, sheep and goats, but this bacterium has also been reported in an increasing number of animal species, including wild reservoirs, such as kangaroos or wallabies in Australia (Stevenson et al., 2015). The main transmission mode to humans is through the inhalation of aerosolized bacteria, even if digestive transmission through unpasteurized dairy products, or tick transmission have been discussed (Eldin et al., 2017). Seasonality and the role of the wind in the transmission of *C. burnetii* have also been discussed (Eldin et al., 2017). Meanwhile, as in this case report, some *C. burnetii* infections have been reported in patients with no risk factors for Q fever. On 8 cases of PJI described (Table 1), only 2 have reported risk factors for Q fever. Furthermore, Q fever was reported for the first time in countries where no animal host has been identified, as in a case of endocarditis in Greenland (Koch et al., 2010). All these observations support the fact that some transmission routes of *C. burnetii* may still need to be elucidated and that risk factors for this infection are not systematically identified. Therefore, in endemic areas like France, PJI diagnostic algorithm should include *C. burnetii* testing for culture-negative samples. This could also be discussed for culture positive PJI with poor evolution, as some chronic Q fever infections associated with dual pathogens have been reported in the literature (Kampschreur et al., 2011).

Few reports of PJI associated with *C. burnetii* have been described in the literature. Of the 8 cases of PJI, 5 have been diagnosed on previously revised arthroplasty (Table 1). In most of these cases, symptoms recorded on admission were pain, swelling or fever. Only one patient had, in addition to local symptoms of pain and swelling, night sweats, headaches and cough (Weisenberg et al., 2017). Thus, the clinical picture of *C. burnetii* PJI seems to be nonspecific in most cases. Therefore, particular attention should be paid to this infection, especially in an endemic epidemiology context where this can lead to an underestimation of this pathology. In osteoarticular infections, a treatment of 18 months by hydroxychloroquine and doxycycline has been suggested as the best option (Eldin et al., 2017). In most of the PJI cases described (5/8), a good clinical evolution has been noticed. However, in 2 cases, after an initial replacement of the joint prosthesis simultaneous to the introduction of the antibiotherapy, a new surgery had to be realized, after 11 weeks and 4 months respectively, following introduction of the antibiotherapy (Million et al., 2014; Weisenberg et al., 2017). In another case, a resection of the arthroplasty and a transfemoral amputation have been achieved (Meriglier et al., 2018). Thus, a severe evolution can be associated with *C. burnetii* PJI and early diagnosis is a key component for the management of these infections.

Culture-negative PJIs remain a significant issue in terms of diagnosis and management. The prevalence of culture-negative PJIs is estimated from 7 to 15% of all PJIs (Tande and Patel, 2014). A major risk factor of culture-negative PJIs is the use of antibiotics that promote a lower sensitivity of standard culture techniques. In the case reported here, the patient did not receive any antimicrobial therapy prior to the hip fluid aspiration. This condition, associated with aspirate purulence and culture negativity, should alert the clinician about the possibility of an unusual microbial pathogen. However, PJIs due to unusual pathogens such as *C. burnetii* are rare, and can be hard to differentiate from other causes of culture-negative PJIs, even in patients who did not receive any antimicrobial therapy: fastidious bacterial pathogens, bacteria included in biofilm (Berbari et al., 2007). Thus, the use of broad spectrum molecular diagnostic techniques can be helpful to discriminate the causes of culture-negative PJIs. Here, the diagnosis was assessed first by 16S rDNA sequencing and then

Table 1
Characteristics of 8 adult patients with description of Prosthetic Joint Infections associated with *Coxiella burnetii*.

Year	Age, sex	Risk factors for Q fever	Surgery history	Clinical features	Specimen	Identification method	Serology	Treatment/Duration	Outcome	Reference
2019	62, M	No	Revised Left Total Hip Arthroplasty	Left hip pain and swelling	Purulent fluid	16S rDNA sequencing and Specific PCR	Positive (phase I IgG ≥ 1:2048 and phase II IgG ≥1:2048, phase I IgM of 1:512 and phase II IgM of 1:64)	Doxycycline and Hydroxychloroquine/ 18 months	Prosthesis loosening, still under antibiotherapy	This case report
2017	64, F	Trip to Cuba with visits to agricultural areas	Bilateral hip and knee replacement	Left knee pain and swelling, night sweats, headaches cough. Infection diagnosis made on left knee prosthesis replacement surgery.	Tissue	Specific PCR	Positive (Phase I IgG of 1:32,768 and phase II IgG of 1:16384, Phase I IgM of 1:16 and Phase II IgM of 1:16)	Doxycycline and Hydroxychloroquine/ 24 months New knee prosthesis replacement 11 weeks after the initial surgery.	Improvement in pain and general symptoms several weeks after treatment introduction, no recurrence of knee pain or systemic symptoms in the several months off antibiotics.	Weisenberg et al. (2017)
2013	63, F	Contact with sheep in Morocco	Revised Left Total Hip Arthroplasty	Left hip pain	Liquid joint	16S rDNA sequencing and Specific PCR	Positive (Phase I IgG of 1:800, IgM negative)	Doxycycline and Hydroxychloroquine/ duration not described Initial removal of the joint prosthesis, replaced by a cement spacer	Spacer explantation at 4 months of treatment	Million et al. (2014)
2012	84, M	Not described	Right Total Hip Arthroplasty	Fever and right hip pain	No	Not performed	Positive (Phase I IgG of 1:1600 and phase II IgG of 1:3200, IgM negative)	Doxycycline and Hydroxychloroquine/ duration not described	Disappearance of pain and scan anomalies during the treatment	Million et al. (2014)
2012	82, M	Not described	Revised Total Hip Arthroplasty	Asymptomatic	Joint aspirate sample	Specific PCR	Serologic increase 3 years after acute Q fever	Doxycycline and Hydroxychloroquine/ duration not described	Good serological evolution under treatment	Million et al. (2014)
2012	60, F	Not described	Left Total Hip Arthroplasty	Left hip pains and low grade fever	Inflammatory pseudo tumor	16S rDNA sequencing and Specific PCR	Positive (Phase I IgG of 1:800 and phase II IgG of 1:1600, IgM negative)	Doxycycline and Hydroxychloroquine/ duration not described	At 12 months of treatment, disappearance of fever and pain, and good serological evolution.	Million et al. (2014)
2013	56, M	No risk context for Q fever, living in an urban area	Revised Total Knee Arthroplasty	Right knee pain and swelling	Periprosthetic tissue Synovial Fluid	Specific PCR Culture on human endothelial cells	Positive (Phase I IgG of 1:4096 and phase II IgG of 1:2048, IgM negative)	Ciprofloxacin and Doxycycline, then Trimethoprim-Sulfamethoxazole and Doxycycline, and then Hydroxychloroquine and Doxycycline/ duration not described	No evidence of relapsed infection 11 months after the initiation of the therapy	Tande et al. (2013)
2018	72, F	No	Total Knee Arthroplasty	Pain, swelling, loosening of the knee prosthesis	Synovial fluid	Specific PCR	Positive	Hydroxychloroquine and Doxycycline/18 months Resection arthroplasty Transfemoral amputation	Not described	Meriglier et al. (2018)

confirmed by specific PCR, corresponding to definite criteria of PJIs based on Eldin's diagnosis algorithm (Eldin et al., 2017). The diagnostic value of 16S rDNA sequencing has been widely discussed in the literature. Some authors, such as Bémer et al., pointed out the lack of sensitivity of this technique, and concluded that 16S rDNA PCR should not be used as a standard procedure in the diagnosis of PJI (Bémer et al., 2014). However, in this last study, within the 215 confirmed PJIs, only 7 had a negative culture result without any antimicrobial therapy. On these, 16S rDNA sequencing was also negative. In this publication, the few numbers of culture negative confirmed PJI were not associated with slow or non-cultivable organisms. However, another study found a detection rate of 26.5% for 16S rDNA sequencing in orthopedic specimens, and 21.7% for standard culture techniques (Grif et al., 2012). In this last publication, discrepant results with positive 16S rDNA PCR result and negative culture were mainly associated with anaerobic, fastidious or noncultivable micro-organisms (Grif et al., 2012). We suggest here that the added value of 16S rDNA PCR should concern not only patients who received antibiotics, but also patients with non-microbiological evidence of infections such as periprosthetic purulence as in this case report. Indeed, molecular methods like 16S rDNA sequencing can be helpful for the diagnosis of rare pathogens such as *C. burnetii* in PJI, and this method should be systematically discussed between bacteriologists and clinicians before evidence of PJI with negative culture, even in the absence of any antimicrobial therapy.

In this case report, *C. burnetii* has been identified as responsible for PJI in an unexpected context. This bacterium should be considered by clinicians as a potential risk in culture-negative PJI cases, especially in endemic diffusion areas.

Conflict of interest

No conflict of interest to declare.

Funding source

None.

Ethical approval

Approval was not required.

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