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Case report

Hip periprosthetic joint infection due to *Coxiella burnetii* in an adult male

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ABSTRACT

Coxiella burnetii is an obligate intracellular Gram-negative bacterium. "Query fever" (Q fever) first described in 1939 is a disease caused by *Coxiella burnetii*. This bacterium infects animals including goats, sheep, and cattle, and has been recognized as a pathogen causing acute illness in humans. A patient living on a farm with a history of a right total hip arthroplasty presented with right hip pain. Arthrocentesis revealed a total nucleated count of 4288 (93% neutrophils), however his synovial fluid culture remained negative. His Q fever phase I IgG and phase II IgG were elevated at 1:4096 and 1:2048, respectively. He underwent incision and drainage with exchange of the femoral head and acetabular component, with retention of the femoral stem. PCR of tissue samples returned positive for *Coxiella burnettii*. He was diagnosed with a persistent localized prosthetic joint infection (PJI) of the right hip. *Coxiella burnetii* PJI is a rare but increasingly recognized form of persistent localized Q fever infection. Q fever should be considered in the differential diagnosis of culture-negative PJI, especially among patients with exposure to sheep, goats, or cattle. Initial screening for *Coxiella burnetii* includes serology, but tissue PCR and immunohistochemical staining may be obtained to confirm joint infection.

Introduction

"Query fever" (Q fever) first described in 1939 is a disease caused by *Coxiella burnetii*. This bacterium infects animals including goats, sheep, and cattle, and has been recognized as a pathogen causing acute illness in humans. Less than 5% of people infected with *C. burnetii* develop persistent localized infections, which can elude detection by conventional bacterial culture techniques. This can result in prolonged and sometimes futile treatment courses. A high degree of suspicion is needed to make the diagnosis. One manifestation of persistent localized Q fever is periprosthetic joint infections (PJI). Here, we describe a case of *C. burnetii* PJI in a 73-year-old man.

Case

In May 2017, a 73-year-old man with type 2 diabetes mellitus and a history of right total hip arthroplasty (THA) in 1996, presented with a 3-month history of progressive right hip pain and a right lateral thigh mass. He denied any fevers, chills, or sick contacts. The patient lived on a farm with sheep, cattle, pigs, and cats. Due to his previous work as an agriculture consultant, he had traveled to numerous countries in Asia, Europe, Africa, and South America.

The patient had a blood pressure of 145/80 mmHg, a heart rate of 66/minute, and a temperature of 36.8 C. His physical examination was significant for a tender 15 × 9 cm mass of the right lateral thigh. His complete blood count (CBC) was within normal limits. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were normal at 7 mm/hr and < 0.5 mg/dL, respectively. Magnetic resonance imaging (MRI) revealed fluid collections around the acetabulum and in the subcutaneous tissue lateral to the hip (Fig. 1). These findings were suspected to be a pseudotumor of the hip. Arthrocentesis of the right hip showed red, turbid fluid with a total nucleated count of 5750 (88% neutrophils). Bacterial, fungal, and mycobacterial cultures from the aspirate yielded no growth. His alpha defensin assay was positive. Metallosis was considered; however, serum levels of titanium, chromium, and cobalt were normal.

The patient underwent incision and drainage (I&D) with an exchange of the femoral head and the polyethylene liner in July 2017.

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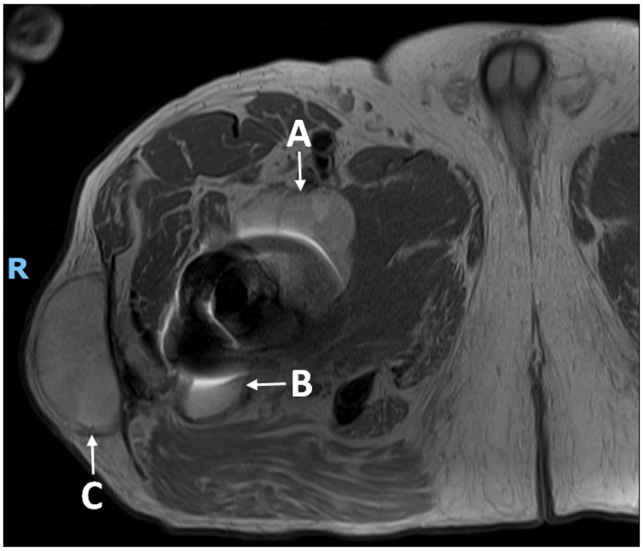

Fig. 1. Magnetic resonance imaging of right pelvis (proton-density weighted). Imaging revealed large fluid collections around the acetabular cup (A), as well as near the proximal femur (B), which was determined to be likely continuous with a subcutaneous fluid collection (C).

Resected tissues were submitted for culture and pathological exam. Histology revealed acute inflammation with > 10 PMNs/HPF. However, tissue cultures yielded no growth. He was diagnosed with a pseudotumor of the right hip with possible culture-negative PJI. He was treated with daptomycin and ciprofloxacin to cover common skin bacteria (e.g., Staphylococcus aureus, coagulase negative staphylococcus) and gram-negative organisms (e.g., pseudomonas), respectively. Serologic testing for Histoplasma, Blastomyces, Coccidioides, Brucella, and Bartonella were negative. Q fever serologies returned positive with a phase I IgG antibody at 1:2048 and phase II IgG antibody at 1:512 (normal <1:16 for both). Intra-operative tissues were also sent to the Mayo Clinic reference laboratories in Rochester, MN for Coxiella polymerase chain reaction (PCR) testing. Interestingly, Coxiella PCR returned negative. Broad range 16 s rRNA PCR with sequencing showed Sphingomonas which was believed to be a contaminant.

In late August 2017 (about 1.5 months after his surgery) the patient was noted to have a large seroma at his surgical site, which subsequently began to drain. The patient underwent yet another I&D with a femoral head and liner exchange. Tissue cultures obtained during surgery again yielded no growth. The patient was continued on daptomycin and ciprofloxacin. He was then seen in the infectious diseases (ID) clinic in October 2017, at which time his incision was well-healed. Antimicrobials were discontinued. The significance of elevated Q fever serologies in a farmer was unknown. Additionally, with a negative PCR and clinical resolution of his infection, it was thought a persistent localized Q fever PJI was unlikely.

However, Coxiella serologies continued to increase during subsequent appointments. In January 2018, his phase I IgG was 1:4096 and phase II IgG was 1:1024. Repeat serologies in April 2018 showed phase I IgG of 1:8192 and phase II IgG of 1:4096. The patient continued to have a well-healed incision with no joint pain and no systemic signs or symptoms of infection. However, given his persistent elevated titers, the patient had additional workup for other causes of persistent localized Coxiella infection including infective endocarditis (IE) and endovascular infection.

A transthoracic echocardiogram (TTE) and transesophageal echocardiogram (TEE) were obtained and revealed no evidence of IE. Numerous sets of blood cultures and serum Coxiella PCR assays were negative. During follow-up in July 2018, his Q fever phase I IgG serologies decreased to 1:4096 and Phase II IgG to 1:2048. Given the patient's decreasing titers, negative workup for persistent localized infection, and lack of any clinical signs of infection, we elected to continue trending Q fever serologies. Unfortunately, the patient was lost to follow up for a few years.

In February 2020 (almost 2.5 years after clinical resolution of hip symptoms), the patient presented with increasing right hip pain and drainage from the incision site. ESR and CRP continued to be normal at 11 mm/hr and 0.4 mg/dL, respectively. He underwent I&D by a local surgeon with cultures yielding no growth. The patient returned to our institution in October 2020 with continued right hip drainage. His physical exam was significant for a sinus tract at the right hip. Arthrocentesis was repeated, revealing a total nucleated count of 4288 (93% neutrophils). His Q fever phase I IgG and phase II IgG continued to be elevated at 1:4096 and 1:2048, respectively. Clinical concern was high for Coxiella PJI. In November 2020, the patient underwent I&D with the exchange of the femoral head and acetabular component with retention of the femoral stem. Per our request, three tissue samples and one synovial fluid sample were again sent to the Mayo Clinic reference laboratories in Rochester, MN for Coxiella PCR testing. Two of three tissue samples returned positive for *Coxiella burnetti*. The patient was diagnosed with a persistent localized *Coxiella burnetti* PJI of the right hip. The subcutaneous fluid collection in right thigh was retrospectively considered as part of his Q fever PJI. Treatment was initiated with doxycycline 100 mg twice daily and hydroxychloroquine (HCQ) 200 mg three times a day.

Since his surgery, the patient is tolerating treatment well and his incision remains well-healed. His most recent phase I IgG titer has remained persistently elevated at 1:8192 as of March 2022. While we suspect he remains chronically infected given the retention of his original femoral stem, he continues to be doing well clinically, including no further drainage from his hip. However, given his titer was still elevated despite 25 months of the treatment, we have decided to continue the combination therapy until we confirm his titer remains consistently low.

Discussion

Coxiella burnetii is an obligate intracellular Gram-negative bacterium. Domestic ruminants (cattle, sheep, and goats) are the most cited host, however other animals and even ticks have been found to carry the bacterium [1]. Transmission can occur via direct contact with infected animals and tick bites [2], however, the most common route of transmission is inhalation of infected aerosols [3]. This occurs via parturient fluid contamination of newborn animals, placenta, wool, and even soil, where it persists in a spore-like form for prolonged periods of time. Winds have been shown to carry contaminated soils as far as 10 km (6.2 miles), resulting in infections without animal exposure [4].

Coxiella infection is asymptomatic in around 60% of cases [5,6]. Patients with acute Q fever commonly report a flu-like syndrome with headaches, myalgias, and abrupt onset of high-grade fevers. Other clinical manifestations of acute Q fever include atypical pneumonia (usually associated with cough and dyspnea) and hepatitis [3]. Persistent localized infection (formerly chronic Q fever) can follow symptomatic or asymptomatic acute infection in 1–5% of patients [12]. The use of the term "chronic Q fever" has been discouraged, with the descriptive term "persistent localized infection" now favored [2]. These localized infections include osteoarticular infection, vascular infection, lymphadenitis, and endocarditis.

C. burnetii osteoarticular infections are uncommon, occurring in about 2% of Q fever cases [2]. This is particularly true of PJI. Such cases present as culture-negative prosthetic joint infections and are often associated with repeated surgeries and antibiotic failure [7]. *C. burnetii* is a rare cause of culture-negative PJI and was initially reported in 1989 by Raoult et al. [8], and later in 2013 by Tande et al. [9]. Since then, Q fever joint infections have been increasingly reported [7,10–15]. This may be attributed to a higher degree of suspicion by clinicians, availability of molecular methods such as PCR, and advanced imaging such as

Table 1
Reported cases of *C. burnetii*-related native or prosthetic joint infection.

Patient age, sex	Joint infected Confirmed vs. probable	Native/ prosthetic	Presenting symptoms	Risk factors	Diagnosis	Surgical intervention	Treatment	Treatment duration	Outcome	Source
7, M	Right hip Confirmed	Native	Fever and back pain	Exposure to goat	Isotope bone scan, serology, mice inoculation, indirect immunofluorescence assay	None	Doxycycline and rifampin	Rifampin: 6 months Doxycycline: 2 years	Resolution of symptoms	Raoult et al. [8]
51, M	Right hip Confirmed	Native	Fever and right hip pain	Exposure to goat	Isotope bone scan, serology	None	Doxycycline	6 months	Decrease of antibody titers	Raoult et al. [8]
56, M	Right knee Confirmed	Prosthetic	Knee pain and effusion, malaise, cough, chills	None listed	Serology and periprosthetic tissue PCR	Resection arthroplasty	Ciprofloxacin (later changed to TMP-SMX, used briefly), doxycycline and hydroxychloroquine	11 months	Resolution of symptoms	Tande et al. [9]
60, M	Right ankle Confirmed	Native	Right ankle swelling and pain	None listed	PCR, indirect immunofluorescence assay (IFA), PET	Tibio tarsal cystectomy	Doxycycline and hydroxychloroquine	18 months	Not described	Angelakis et al. [12]
53, F	Left shoulder Confirmed	Native	Shoulder swelling and weight loss	Farm exposure, immunosuppression (methotrexate)	PCR, IFA, PET	None	Doxycycline and hydroxychloroquine	18 months	Not described	Angelakis et al. [12]
60, F	Left hip Confirmed	Prosthetic	Left hip pain, fever, pseudo-tumor	None listed	Serology and periprosthetic tissue PCR	Hip revision	Doxycycline and hydroxychloroquine	At least 12 months	Resolution of fever and pain	Million et al. [7]
82, M	Right hip Confirmed	Prosthetic	Asymptomatic	None listed	Serology, PET, PCR	None	Doxycycline and hydroxychloroquine	Not listed	Improved titers	Million et al. [7]
84, M	Right hip Confirmed	Prosthetic	Fever and right hip pain	None listed	Serology, PET	None	Doxycycline and hydroxychloroquine	Not listed	Improved titers, pain resolution	Million et al. [7]
63, F	Left hip Confirmed	Prosthetic	Left hip pain	Exposure to sheep	Serology and joint fluid PCR	Resection arthroplasty with cement spacer	Doxycycline, hydroxychloroquine	4 months	Spacer explantation	Million et al. [7]
67, M	Right sternoclavicular joint Confirmed	Native	Fever, confusion	None listed	Serology, PET	None	Doxycycline and hydroxychloroquine	18 months	Four-fold decrease in titers	Angelakis et al. [10]
64, F	Left knee Confirmed	Prosthetic	Left knee pain and swelling, malaise, night sweats	Trip to Cuban agricultural areas	Serology and periprosthetic tissue PCR	Two-stage exchange	Doxycycline and prosthesis removal	"Several months"	Resolution of symptoms, decreased titers	Weisenberg et al. [14]
64, F	Right acromioclavicular joint and left hip Confirmed	Native	Right shoulder and left buttock pain	Immunosuppression (steroid, nilotinib)	Serology, PET, and synovial and bone biopsy PCR	None	Doxycycline and hydroxychloroquine	18 months	Fever and pain resolution	Melenotte et al. [11]
72, F	Knee Confirmed	Prosthetic	Pain, swelling, and loosening of knee prosthetic	None listed	Serology, joint fluid PCR	Resection arthroplasty, transfemoral amputation	Doxycycline and hydroxychloroquine	18 months	Not described	Meriglier et al. [15]
62, M	Left hip Confirmed	Prosthetic	Hip pain and swelling	None listed	Serology and PCR	None	Doxycycline and hydroxychloroquine	24 months	Resolution of hip pain and swelling	Chenouard et al. [13]
52, M	Right hip Probable	Native	Right thigh pain	Exposure to cow tissues	Serology	Two-stage exchange	Doxycycline and hydroxychloroquine	36 months	Resolution of symptoms, decreased titers	McKew et al. [19]
65, F	Left hip Confirmed	Prosthetic	Fever and left hip pain	Immunosuppression (methotrexate, tumor	Serology and PCR	Two-stage exchange	Ofloxacin and rifampin	18 months	Resolution of symptoms,	Miailhes et al. [20]

(*continued on next page*)

Table 1 (*continued*)

Patient age, sex	Joint infected Confirmed vs. probable	Native/ prosthetic	Presenting symptoms	Risk factors	Diagnosis	Surgical intervention	Treatment	Treatment duration	Outcome	Source
				necrosis factor-alpha blocker)					decreased titers	
73, M	Right hip Confirmed	Prosthetic	Right hip pain and swelling	Exposure to farm animals	Serology and tissue PCR	Exchange of femoral head and acetabular component	Doxycycline and hydroxychloroquine	Ongoing, currently 25 months	Resolution of symptoms	This current report

Abbreviations:
PCR: Polymerase chain reaction
PET: Positron emission tomography
IFA: Immunofluorescence assay.

positron emission tomography (PET) scans. The diagnosis of Q fever is usually made by serologic testing for antibodies to phase I and II antigens [16,17]. Acute Q fever is diagnosed by a 4-fold increase in anti-phase II IgG or by a single-phase II IgG titer ≥ 1:128 or an elevated phase II IgM in the appropriate clinical setting. Anti-phase I IgG at titers of ≥ 1:800 are indicative of persistent localized Q fever [16,17]. Therefore, patients with serological evidence of persistent localized Q fever should have an aggressive search for the site of infection. The diagnosis also can be made using molecular methods including 16S ribosomal ribonucleic acid (rRNA) PCR amplification plus sequencing or with specific *C. burnetii* PCR [16]. Culture is restricted to specialized laboratories [16,17]. 18-FDG-PET-CT has helped identify vascular infections, endocarditis, joint infections, and other local *C. burnetii* infections and to assess the response to therapy [17]. Confirmation of Q fever joint infection is usually obtained with PCR, 16S ribosomal RNA PCR amplification, immunohistochemistry of either joint fluid or periprosthetic tissues, and very rarely culture. However, per Angelkais et al., 16S rRNA gene amplification with sequencing (which we initially performed in this patient) has lower sensitivity than *C. burnetii*-specific PCR tests. Thus, a negative test cannot exclude infection due to *C. burnetii* [12]. As with this case, if there is a high index of suspicion for *C. burnetii*, multiple samples of different tissue types should be submitted for PCR testing.

We searched for articles about *C. burnetii*-related joint infections in English using PubMed and Google Scholar with the terms "*Coxiella burnetii,*" "Q fever," "chronic infection," "persistent infection," "prosthetic joint infection," and "osteoarticular infection." We excluded diskitis or spinal infection due to Q fever. This revealed 22 cases, including 7 pediatric cases reported in a case series [8,9,12,7,10,14,11,15,13,18–20]. Among them, detailed information was available for 16 cases (summarized in Table 1). The median age was 62.5 years (range 7–84) and male gender was reported in 9 of 16 (56%) cases. There were 9 cases of PJI, 7 of which occurred in the hip. Treatment was similar between identified cases, with the majority (12/16, or 75%) using a combination of doxycycline and hydroxychloroquine. Treatment durations lasted 6 months to 3 years based on reported data (3 cases did not have clearly stated durations). Most cases resulted in resolution, with an unfavorable outcome in only 1 case (repeat surgery with spacer explantation).

Acute Q fever is managed with doxycycline (200 mg daily) if patients present with symptomatic disease. In cases of persistent localized infection, patients should be treated with prolonged courses of doxycycline and hydroxychloroquine. Currently, no cohort study has been conducted to guide *C. burnetii* PJI treatment, however at least an 18-month course of doxycycline and hydroxychloroquine has been recommended [2].

Conclusions

Coxiella burnetii PJI is a rare but increasingly recognized form of persistent localized Q fever infection. Persistently elevated Coxiella Phase I IgG titers increased our suspicion of a persistent localized infection. Detection of Coxiella by PCR analysis in synovial tissue helped confirm a diagnosis of Coxiella PJI. Q fever should be considered in the differential diagnosis of culture negative PJI, especially among patients with animal exposure to sheep, goats, or cattle. Treatment of *Coxiella burnetii* PJI includes prolonged doxycycline in combination with hydroxychloroquine.

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Ethical approval

The local ethical committee approval does not apply in this case.

Consent

The patient's written consent was obtained.

CRediT authorship contribution statement

Ian Kidder: Writing – original draft, Writing – review & editing. **Takaaki Kobayashi:** Writing – review & editing, interpretation of results. **Bradley Ford:** Writing – review & editing, final approval of the version to be submitted, interpretation of results. **Poorani Sekar:** Conceptualization, Writing – review & editing, Supervision, final approval of the version to be submitted, interpretation of results.

Declarations of interest

None.

References

[1] Mancini F, Di Luca M, Toma L, et al. Prevalence of tick-borne pathogens in an urban park in Rome, Italy. Ann Agric Environ Med 2014;21(4):723–7.
[2] Eldin C, Melenotte C, Mediannikov O, et al. From Q fever to Coxiella burnetii infection: a paradigm change. Clin Microbiol Rev 2017;30(1):115–90.
[3] Maurin M, Raoult D, fever Q. Clin Microbiol Rev 1999;12(4):518–53.
[4] Clark NJ, Soares Magalhaes RJ. Airborne geographical dispersal of Q fever from livestock holdings to human communities: a systematic review and critical appraisal of evidence. BMC Infect Dis 2018;18(1):218.
[5] Bacci S, Villumsen S, Valentiner-Branth P, Smith B, Krogfelt KA, Molbak K. Epidemiology and clinical features of human infection with Coxiella burnetii in Denmark during 2006-07. Zoonoses Public Health 2012;59(1):61–8.
[6] Raoult D, Marrie T, Mege J. Natural history and pathophysiology of Q fever. Lancet Infect Dis 2005;5(4):219–26.
[7] Million M, Bellevegue L, Labussiere AS, et al. Culture-negative prosthetic joint arthritis related to Coxiella burnetii. Am J Med 2014;127(8). 786 e7- e10.
[8] Raoult D, Bollini G, Gallais H. Osteoarticular infection due to Coxiella burnetii. J Infect Dis 1989;159(6):1159–60.
[9] Tande AJ, Cunningham SA, Raoult D, Sim FH, Berbari EF, Patel R. A case of Q fever prosthetic joint infection and description of an assay for detection of Coxiella burnetii. J Clin Microbiol 2013;51(1):66–9.
[10] Angelakis E, Thiberville SD, Million M, Raoult D. Sternoclavicular joint infection caused by Coxiella burnetii: a case report. J Med Case Rep 2016;10(1):139.
[11] Melenotte C, Bart G, Kraeber-Bodere F, Cammilleri S, Le Goff B, Raoult D. Isolation of Coxiella burnetii from an acromioclavicular infection with low serological titres. Int J Infect Dis 2018;73:27–9.
[12] Angelakis E, Edouard S, Lafranchi MA, Pham T, Lafforgue P, Raoult D. Emergence of Q fever arthritis in France. J Clin Microbiol 2014;52(4):1064–7.
[13] Chenouard R, Hoppe E, Lemarie C, et al. A rare case of prosthetic Joint Infection associated with Coxiella burnetii. Int J Infect Dis 2019;87:166–9.
[14] Weisenberg S, Perlada D, Peatman T. Q fever prosthetic joint infection. BMJ Case Rep 2017:2017.
[15] Meriglier E, Sunder A, Elsendoorn A, et al. Osteoarticular manifestations of Q fever: a case series and literature review. Clin Microbiol Infect 2018;24(8):912–3.
[16] Anderson A, Bijlmer H, Fournier PE, et al. Diagnosis and management of Q fever–United States, 2013: recommendations from CDC and the Q Fever Working Group. MMWR Recomm Rep 2013;62(RR-03):1–30.
[17] Ernest V, Cammilleri S, Amabile P, et al. Hemodialysis vascular graft as a focus of persistent Q fever. Infection 2018;46(6):881–4.
[18] Sachs N, Atiya-Nasagi Y, Beth-Din A, et al. Chronic Q fever infections in Israeli children: a 25-year nationwide study. Pediatr Infect Dis J 2018;37(3):212–7.
[19] McKew GL, Gottlieb T. Reactivation of Q fever: case report of osteoarticular infection developing at the site of a soft tissue injury. Access Microbiol 2021;3(12): 000296.
[20] Miailhes P, Conrad A, Sobas C, et al. Coxiella burnetti prosthetic joint infection in an immunocompromised woman: iterative surgeries, prolonged ofloxacin-rifampin treatment and complex reconstruction were needed for the cure. Arthroplasty 2021;3(1):43.