CASE REPORT

Q fever prosthetic joint infection

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SUMMARY

Coxiella burnetii is the causative pathogen of the zoonotic infection Q fever. Most patients with Q fever experience a non-specific febrile illness, hepatitis or pneumonia. Q fever has recently been described as a cause of prosthetic joint septic arthritis, but remains very uncommonly reported. We present a case of Q fever prosthetic joint septic arthritis that has responded to a combination of two-stage surgical exchange and prolonged medical treatment with doxycycline and hydroxychloroquine.

BACKGROUND

Q fever is a zoonotic infection caused by the bacterium *Coxiella burnetii*. Infection is asymptomatic in over half of infected individuals. Patients showing symptoms may present acutely with a non-specific febrile illness, hepatitis, pneumonia or a chronic focal persistent infection such as endocarditis.¹

Prosthetic joint infection (PJI) affects a minority of patients who receive joint replacements, but requires one or more surgeries and prolonged antimicrobials to cure. Optimal management of PJI requires identification of the pathogen.²

C. burnetii was recently described as a cause of PJI, but only a few cases have been described to date in the literature.^{3–5} Here we present a case of Q fever PJI in a woman who recently travelled.

CASE PRESENTATION

A 64-year-old woman presented with progressive left knee pain and swelling. Her medical history included bilateral knee and hip replacements, but she was otherwise healthy. The left knee replacement was performed 15 years prior to this episode. She had some left knee pain for several years, but the pain worsened for several months. She also experienced non-drenching night sweats, headaches, occasional cough and a feeling of being unwell for several months. These systemic symptoms started several weeks after a trip to Cuba that included visits to agricultural areas. Other travel in the last year included a trip to the Netherlands.

She was initially admitted for an elective left knee revision surgery. On opening the knee, murky odorous fluid was encountered and the synovium had a green discolouration. A fungating, cauliflower-like tissue was seen in the suprapatellar region. Intraoperative Gram stains of the periprosthetic tissue did not reveal any organisms, and white cell count in the joint fluid was only 200 cells/ μ L. The surgical plan was changed to a two-stage exchange,

and a vancomycin impregnated spacer was inserted after surgical cleanout and debridement of the knee. Aerobic and anaerobic cultures remained negative after 14 days from three tissue specimens and two joint fluid specimens. Mycobacterial and fungal cultures were negative. Histopathology of periprosthetic tissue showed chronic inflammation with a foreign-body giant cell reaction and a lymphohistiocytic infiltrate. She was treated empirically with vancomycin, ceftriaxone and metronidazole for presumed culture-negative PJI. The baseline sedimentation rate was 43 and C reactive protein was 3.1 mg/L (normal range 0–9 mg/L). Liver function tests were within normal limits and a chest X-ray was unremarkable.

She completed her course of empiric antibiotics. Doxycycline was added after an elevated *C. burnetii* titre. However, doxycycline was held for 2 weeks before a planned second-stage surgery to obtain fresh cultures of antimicrobials.

Surgery to place a new left knee prosthesis was performed 11 weeks after the initial surgery. No signs of infection were seen, and the prior findings had resolved. Multiple tissue specimens again did not grow under aerobic and anaerobic conditions held for 14 days, and repeat acid-fast bacilli and fungal cultures were negative. Doxycycline alone was resumed immediately after the surgery while additional studies were pending.

INVESTIGATIONS

With the prodromal systemic symptoms and negative initial cultures, additional aetiologies were considered at the time of the first surgery. QuantiFERON Gold, beta-D-glucan, coccidioides serology and Brucella serology were all negative, among other tests. A Q fever serology was reactive with a phase I IgG immunofluorescence assay IgG titre of 1:32 768 and a phase II IgG titre of 1:16 384. (Focus Diagnostics, San Juan Capistrano, California, USA). IgM antibodies were 1:16 for both phase I and phase II (borderline positive).

Fixed tissue from the initial surgery, as well as fresh tissue from the second surgery, were submitted to the Center for Disease Control and Prevention (CDC) for analysis for *C. burnetii*. All tissues were negative on immunohistochemical staining. Multiple fixed tissues, as well as a fresh specimen, were positive for *C. burnetii* by PCR.

A transthoracic echocardiogram showed no valvular dysfunction or vegetations, and remained unchanged on follow-up. She was unable to tolerate a transoesophageal echocardiogram.

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DIFFERENTIAL DIAGNOSIS

The initial differential diagnosis included the usual causes of PJI, including *Staphylococcus aureus*, coagulase-negative *Staphylococcus* and Gram-negative bacteria. The negative cultures raised concern for other causes of culture negative PJI, including mycobacterial and fungal disease. Reports of Q fever as a cause for PJI,³ as well as her systemic symptoms, prompted testing for *C. burnetii*.

TREATMENT

She was treated with doxycycline and hydroxychloroquine for 24 months, in addition to the two surgeries listed previously.

OUTCOME AND FOLLOW-UP

Within several weeks of starting doxycycline after the first surgery, she noted a significant improvement in her overall sense of well-being, with resolution of her headaches and sweats. Her knee recovered after the second surgery, and she had no pain, swelling or other signs of infection. Q fever titres in the immediate postoperative period after the second surgery were elevated, with a phase I titre of 1:32 798 and a phase II titre of 1:8192. Titres gradually improved in the following months. IgM titres became negative. She has had no recurrence of knee pain or systemic symptoms in the first several months off antibiotics, though she will require serological and clinical monitoring for relapse for at least 5 years.⁶

DISCUSSION

C. burnetii is found in a wide variety of mammals, reptiles, birds and ticks.⁷ Human infection occurs via inhalation of aerosolised bacteria from birth products, urine, faeces and other infected material. Other potential routes of infection include unpasteurised milk ingestion and tick bites. People in close contact with animal products, including farm workers and slaughterhouse workers, are at an increased risk. However, aerosolisation can lead to infections in inhabitants or visitors to endemic areas without any direct animal contact.⁸

C. burnetii has only recently been recognised as a cause of PJI. Tande and colleagues reported a 56-year-old man with several year history of suspected PJI eventually diagnosed with Q fever.³ Million and colleagues subsequently reported four patients from France with Q fever PJI.⁴ One patient was found to have an inflammatory pseudotumour on histopathology. One patient was diagnosed with asymptomatic prosthetic hip septic arthritis 3 years after a case of Q fever. One patient developed a left hip prosthetic infection 3 weeks after exposure to sheep. One patient presented with fever and hip pain. Lastly, Eldin and colleagues used positron emission tomography CT to identify foci of infection in patients with Q fever, and found three others with PJI.⁵ Thus, Q fever PJI may present with both acute and chronic joint symptoms and may be asymptomatic.

It is unclear exactly where the case patient was infected. Her symptoms began shortly after a trip to Cuba where she visited rural agricultural areas. *C. burnetii* was recently described in ticks in Cuba.⁹ The incubation period of ≥ 2 –3 weeks⁶ and visits to agricultural areas would be consistent with infection acquired in Cuba. However, she was also in the Netherlands several months prior to the Cuba trip. Her visit to the Netherlands included areas involved in the prolonged Q fever outbreak in that country.¹⁰ Aerosol is the most likely means of infection⁷ though an unnoticed tick bite cannot be excluded.

Diagnosis of Q fever may be done by serology, nucleic acid detection or immunohistochemical staining of the infected

tissue. *C. burnetii* will not grow on routine laboratory culture media. Culture is not attempted by most clinical laboratories and require a biosafety level 3 laboratory to protect laboratory personnel.⁶ Clinicians considering Q fever will typically start with a serological investigation, including phases I and II *C. burnetii* antibodies.¹¹ Patients with persistent focal or 'chronic' Q fever will typically have elevated phase I titres. Patients with serological evidence of chronic Q fever should have an aggressive search for the site of infection.⁷ Criteria for Q fever PJI diagnosis have been proposed.⁴ The described patient herein meets criteria for a 'definite' case of Q fever PJI based on the positive PCR result from the infected periprosthetic tissue.

Treatment options for Q fever PJI mimic those for Q fever endocarditis. Doxycycline is the drug of choice, though moxifloxacin, levofloxacin, trimethoprim-sulfamethoxazole and rifampin (in combination) are all efficacious. Hydroxychloroquine is added to alkalinise the endosome and restore the bactericidal effect of doxycycline against *C. burnetii*. A combination of doxycycline and hydroxychloroquine, as opposed to doxycycline alone, is necessary to minimise any relapse risk.¹²

Prosthetic joint infection complicates 0.5–1.5 percent of knee and hip replacement surgeries. Seven to 15% of PJI are culture negative.¹³ While many of these culture negative cases are associated with prior antimicrobial use, or inability to isolate known pathogens, an unknown number are associated with pathogens typically not included in the microbiological differential diagnosis of PJI. Risk factors for *C. burnetii* should be sought in patients with culture negative PJI, and appropriate testing initiated.

Learning points

- *Coxiella burnetii* risk factors should be sought in patients with prosthetic joint infection, particularly if initial joint cultures are negative.
- Initial screening for *C. burnetii* includes serology, but tissue PCR and immunohistochemical staining can be pursued to confirm diagnosis.
- Treatment of *C. burnetii* prosthetic joint infection may be accomplished with surgery plus prolonged doxycycline in combination with hydroxychloroquine.

Contributors All authors: participated in care of the patient and manuscript editing. SW: responsible for the accuracy of the clinical description.

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