CASE REPORT

Bartonella Quintana prosthetic aortitis successfully treated with doxycycline

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SUMMARY

Bartonella quintana is a rare cause of culture-negative endovascular infection, characterised by intracellular persistence. We describe a case of ascending aortic prosthetic graft infection due to *B. quintana*, in a patient with past unrecognised necrotising aortitis, which was successfully treated with doxycycline monotherapy.

BACKGROUND

Since its discovery as the causative agent for trench fever, *Bartonella quintana* has re-emerged as a significant pathogen causing 'culture-negative' endocarditis and endovascular infections. Diagnosis requires clinician awareness, given it is difficult to culture, and requires species-specific serology or PCR. This is the first case of *B. quintana* causing prothetic endovascular graft infection, which raised novel management dilemas regarding the duration of therapy for this infection.

CASE PRESENTATION

A 70-year-old woman presented with 2 months of fever, drenching night sweats and 7 kg weight loss. She was born in Greece with exposure to domestic animals and crowded living conditions, but had migrated to Australia over fifty years ago. Her past medical history included ischaemic heart disease and an ascending aortic aneurysm of hitherto unknown aetiology which resulted in uncomplicated coronary artery bypass grafting, aortic valve repair and ascending aortic aneurysm replacement with a polyethylene terephthalate (Dacron) graft 4 years prior.

On examination she was febrile (39.3°C) with other vital signs in the normal range. A temperature chart in hospital recorded daily fever that peaked during the evening hours. There were no peripheral stigmata of endocarditis and no audible murmurs. There was no added breath sounds, lymphadenopathy or organomegaly. The patient was hospitalised for further investigation; no empirical antimicrobials had previously been prescribed.

INVESTIGATIONS

The C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) were elevated at 38 mg/L (reference range (RR) <3.1 mg/L) and 58 mm/hour (RR 0 to 15 mm/hour), respectively. Multiple peripheral blood cultures were negative after extended incubation and HIV and *Treponema pallidum* serology was negative. Transthoracic and transoesophageal echocardiography demonstrated no evidence of endocarditis; there was mild aortic regurgitation and normal biventricular function. CT revealed no source of infection in the sinuses, neck, chest, abdomen or pelvis, however subsequent whole-body positron-emission tomography (PET) showed marked fluorodeoxyglucose (FDG) activity in the ascending aorta involving the Dacron graft (figure 1A) as well as low-grade symmetric hilar and mediastinal lymph node uptake and diffuse splenic uptake (figure 1B). As biopsy of the prosthetic ascending aorta was not possible, mediastinal lymph node biopsy via endobronchial ultrasound was obtained but histology and culture were non-diagnostic. Mycobacterial PCR on serum and mycobacterial blood cultures were negative. Throughout these investigations the patient remained antibiotic-naïve.

A presumptive serological diagnosis was obtained after *B. quintana* IgG was markedly elevated at a titre of 1:4096 (non-reactive <1:64) on immunofluorescence serology. Low-titre IgG positivity to *Bartonella henselae* of 1:256 (non-reactive <1:64) was also observed and thought to represent cross-reacting antibody. *Bartonella* real-time PCR targetting the *ssrA* gene on serum was negative.[1]

On review of the histology of the native ascending aortic aneurysmal tissue from 4 years prior, there was evidence of necrotising aortitis with associated giant cells, chronic periaortitis and medial degeneration. The patient described a febrile illness of 6 months duration 16 years prior, which resembled the current illness. *Bartonella* PCR targeting the ssrA gene performed on the paraffin section from the aortic aneurysmal tissue 4 years prior was negative.

TREATMENT, OUTCOME AND FOLLOW-UP

The patient was treated with oral doxycycline 100 mg 12-hourly with resolution of fever and night sweats within 24 hours. The patient was discharged home, and on review 6 weeks later the patient remained afebrile with a repeat PET showing marked reduction of FDG avidity in the ascending aortic graft (figure 1C) with near-complete resolution of previously avid mediastinal lymph nodes and spleen (figure 1D). Doxycycline was reduced to 100 mg daily with a plan for lifelong low-dose suppressive doxycycline therapy due to the patient's age and the risk of relapse of the chronic prosthetic graft infection. One year after diagnosis she remains well with a CRP and ESR of 1 mg/L (RR <3.1 mg/L) and 14 mm/hour (RR 0 to 15 mm/hour) respectively; however repeat PET at

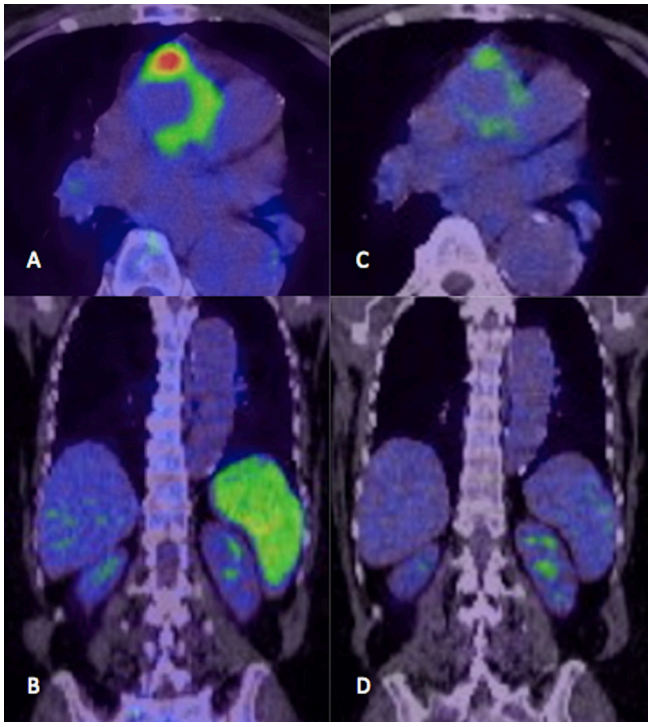

Figure 1 Positron-emission tomography demonstrating (A) marked fluorodeoxyglucose uptake involving the ascending aortic prosthetic graft, (B) moderate uptake of the spleen, (C) interval improvement in aortic graft uptake and (D) resolution of splenic uptake after 6 weeks of doxycycline treatment.

this time showed persistent (although improved) FDG activity in the region of the aortic graft.

DISCUSSION

We report a unique case of prosthetic aortitis caused by *B. quinana* treated with doxycycline monotherapy. Previous case reports of *Bartonella* aortitis are limited,[2] while prosthetic graft infection has been reported with *B.henselae,*[3] there are no reports of prosthetic endovascular graft infection due to *B. quintana*. *B. quinana* is one of two species of *Bartonella* which exists in humans as the reservoir host.[4] It was the pathogen responsible for trench fever, a protracted febrile illness described in the first World War,[5] and has subsequently been observed to cause outbreaks of bacteraemia as well as endocarditis in urban homeless populations.[6] Pathogenesis involves transmission by an arthropod vector (most commonly the human body louse) via broken skin with uptake of *Bartonella* in a primary intracellular niche which evades the host immune response with subsequent intermittent seeding into the bloodstream where bartonellae inhabit erythrocytes.[7] In its reservoir host, *Bartonella* can persist and cause chronic asymptomatic infection and persistent bacteraemia.[6 7] In the current case, the patient may have acquired *B. quintana* many years ago, possibly causing her undiagnosed 6-month febrile illness (likely trench fever), resulting in persistent bacteraemia and native ascending aortic aneurysm with subsequent reseeding her aortic graft.

Serological detection of the presence of *Bartonella* IgG is the most common method of making a diagnosis in patients with a clinically compatible syndrome. In patients with culture negative endocarditis, the presence of a *Bartonella* IgG titre of >1:800 had 95% positive predictive value for a diagnosis of *Bartonella* endocarditis.[8] *Bartonella* endocarditis is associated with inducing high IgG antibody titres (>1:800) due to the repeated showering of bacteria into the circulation and therefore high antibody titres should theoretically also be present in non-endocarditis endovascular infection. *Bartonella* serology is limited by significant rates of cross-reactivity within *Bartonella* species and between other similar species.[6] For example, in 258 patients with confirmed Q fever endocarditis, cross-reactivity was observed in over 50% of cases who had antibodies that reacted against *B. henselae.*[9] However, the cross-reacting antibodies generally have low titers and clinicians must therefore interpret low-titre *Bartonella* antibody results with caution to avoid misdiagnosis, and consider testing serology for other similar organisms such as Q fever. Although no serological assay is truly species-specific, the laboratory should test the patient serum against antigens of both *B.quintana* and *B.henselae* to avoid misdiagnosis, as may have occurred in our case had only *B. henselae* serology been performed. The other limitation of serological diagnosis in patients with possible bartonellosis is that commercial serology is confined to a small number of *Bartonella* species known to cause human infection. Most commonly this includes *B. henselae* and *B. quintana,* however a further 12 species of *Bartonella* are known to cause human infection.[10]

Other diagnostic methods of detecting the micro-organism are limited by poor sensitivity. Peripheral blood cultures have a sensitivity of approximately 25% in patients with *Bartonella* endocarditis, even when extended incubation at 35°C–37°C occurs.[8] A variety of PCR targets have been developed, and in general infected tissue is required to reach limits of detection rather than blood. A nested PCR has been developed with sensitivity of 58% in serum of patients with *Bartonella* endocarditis.[11] In the current case, *Bartonella* real time non-nested PCR on serum was unsurprisingly negative. Therefore we attempted to retrospectively perform PCR on the paraffin section from the original aneursymal tissue from fours years prior. Unfortunately *Bartonella* PCR on this fixed tissue was negative, which may be due to breakdown of DNA by formalin used to fix the tissues.

The optimal antimicrobial treatment of *Bartonella* aortitis is largely unknown, and relies heavily on data from *Bartonella* endocarditis. From a large retrospective cohort of 101 patients with *Bartonella* endocarditis, receipt of an aminoglycoside in addition to another antibiotic (such as a beta-lactam or doxycycline) was associated with increased likelihood of recovery compared with patients who did not receive an aminoglycoside.[12] These findings led to the current recommendations of a 2-week course of gentamicin (3 mg/kg per 24 hours in three divided doses) in addition to a 6-week course of doxycycline (100 mg twice-daily) for the treatment of confirmed *Bartonella* endocarditis, with the substitution of gentamicin for rifampicin (300 mg twice-daily) in those where aminoglycosides are contraindicated.[13] In the current case, doxycyclne monotherapy was successfully used, without the use of gentamicin or rifampicin. The decision not to give a second agent was made due to: (1) the patient's pre-existing symptoms of peripheral vertigo which may have been exacerbated with gentamicin, (2) the marked recovery of the patient with doxycycline alone prior to rifampicin being considered and (3) due to the prolonged nature of therapy due to graft involvement, so an additional agent for a short period was felt to not be required.

The optimal duration of antmicrobial therapy in patients with retained *Bartonella* endovascular graft infection is not known. However, the ability of *Bartonella* species to form biofilm is well-documented,[14] and therefore we hypothesise that complete microbiological cure may be difficult where a prosthetic graft has been infected and cannot be surgically removed. Biofilm

production in *B. henselae* and *B. quintana* appears to be dependent on surface adhesins such as *Bad-A* which are responsible for adherence to the extracellular matrix, autoagglutination and inducing a proangiogenic host response.[14] In the current case, the patient was identified for a long course of suppressive doxycycline given the risk of relapse without removal of the graft which, given her age and operative risk, has not been considered.

In conclusion, this is the first-reported case of prosthetic aortitis due to *B.quintana* in a patient with a prolonged fever of unknown origin and previous histologically proven necrotising aortitis. The diagnosis was confirmed using serology against the two Bartonella species known to cause infection in Australia. monotherapy with doxycycline led to a very rapid clinical improvement and dramatic FDG-PET improvement in aortic, lymph node and splenic uptake. Clinicians must be cautious when ordering *Bartonella* serology in patients with compatible symptoms, as the diagnosis may be missed or attributed to an incorrect species if only *B. henselae* serology is performed.

Learning points

- *Bartonella quintana* is a rare cause of culture negative endovascular infection, which is capable of causing prosthetic graft infections.
- Laboratories should test serum against antigens of both *B.quintana* and *Bartonella henselae* to avoid misdiagnosis and clinicians should interpret low-level *Bartonella* antibody titres with caution due to high rates of cross-reacting antibodies.
- In patients with *Bartonella* endovascular graft infection who are not candidates for graft removal, long-term doxycycline monotherapy represents a viable suppressive therapy.

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