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CASE REPORT

# An unexpected case of *Bartonella alsatica* prosthetic vascular graft infection

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**Abstract:** *Bartonella alsatica* is a wild rabbit pathogen causing bacteremia rarely reported in humans, with only three cases published so far, including one lymphadenitis and two endocarditis cases. Here, we report the case of a 66-year-old man who suffered from acute renal failure due to a membranoproliferative glomerulonephritis. Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) showed diffuse FDG uptake around the aortobifemoral graft with no indication of infection. A white blood cell scan showed an accumulation of labeled neutrophils on the left femoral part of the graft. The patient underwent surgery and an abscess around the left iliac part of the graft was found intraoperatively. Intraoperative samples were all negative, but 16S rRNA gene-based PCR was positive, and the sequence was positioned among the *Bartonella* species cluster. Specific PCRs targeting *gro*EL/*hsp*60, *rpo*B and *glt*A genes were performed and led to the identification of *B. alsatica*. Accordingly, indirect immunofluorescence serological analyses were positive for *Bartonella henselae* and *Bartonella quintana*. The patient had a history of regularly hunting wild rabbits. He was treated with 100 mg of doxycycline twice a day for six months and his renal function significantly improved with no sign of persistent infection. This case highlights the contribution of serology assays and molecular-based methods in prosthetic vascular graft infection diagnosis.

**Keywords:** vascular graft infection, *Bartonella alsatica*, 16S rRNA PCR, membranoproliferative glomerulonephritis

## Introduction

*Bartonella* species are fastidious, aerobic or microaerophilic, Gram-negative and facultative intracellular bacteria.[1] *Bartonella* spp. are usually responsible for lymphadenitis and endocarditis. Diagnosis is often difficult and requires the use of serological assays and molecular-based methods.[1] Only three cases of *B. alsatica* infection in humans have been reported so far, one lymphadenitis[2] and two endocarditis[3] cases. Although two cases of prosthetic vascular graft infection (PVGI) caused by *B. henselae* were previously reported,[4] this is the first case of PVGI associated with *B. alsatica* and therefore the fourth human case of *B. alsatica* infection.

## Case

A 66-year-old man with an aortobifemoral bypass was admitted to the nephrology department of Périgueux Hospital, France, in November 2016 for acute renal failure (serum creatinine 4.8 mg/dL *versus* 2.3 mg/dL in October 2016). He had an undiagnosed chronic renal failure evolving since 2013. The patient showed a global cardiac

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insufficiency and asthenia; he had macroscopic hematuria, lower limb oedema, and one episode of low grade fever during hospitalisation. Biological signs of inflammation were minimal (CRP 18 mg/L (normal value <5 mg/L), neutrophils 5.6 G/L). He had low serum albumin (3.1 g/dL) and glomerular proteinuria (urine protein-creatinine ratio 14 g/g). A renal biopsy showed a membranoproliferative glomerulonephritis, with marked granular subendothelial and mesangial deposits of IgM, C1q, C3 and IgG, and two spots with extracapillary proliferation. Blood cultures, autoimmune assays, cryoglobulinemia, HIV, HBV, and HCV serologies were negative. Trans-thoracic echocardiography showed no sign of endocarditis. Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) showed diffuse FDG uptake around the graft with no indication of infection. The left femoral part of the graft was considered to be infected based on white blood cell scan images. Renal function improved slightly after diuretic treatment (serum creatinine 3.2 mg/dL, urine protein-creatinine ratio of 6 g/g).

Subsequently, the patient was admitted to Bordeaux University Hospital, France, in February 2017 with a high suspicion of PVGI, considering the previous episode of low grade fever, the slightly elevated biological signs of inflammation and the signs of infection in the left femoral part of the graft based on white blood cell scan images. In May 2017 he underwent surgery. An abscess around the left iliac part of the graft was found intraoperatively. The graft was replaced by a new graft made of silver-triclosan knitted collagen-coated polyester. The patient was treated postoperatively with meropenem, linezolid, caspofungin and amikacin. All of the intraoperative samples were negative. Only one sample from the right iliac part of the graft was positive for *Staphylococcus pasteuri*, which was considered to be a contaminant. *Coxiella burnetii* serology was negative. No multi-drug resistant bacterium was isolated and antimicrobial therapy was changed to piperacillin-tazobactam. Since cultures of graft specimens were negative, a 16S rRNA gene-based PCR with subsequent sequencing was performed.[5] The Bioinformatics Bacterial Identification tool (BIBI)[6] positioned the primer-less 16S rRNA sequence (GenBank accession number: MH230166) among the *Bartonella* species cluster. The identification at the species level was then performed using specific PCRs targeting *groEL/hsp60, rpoB* and *gltA* genes since these genes have the best discriminating power among the *Bartonella* species. The BIBI positioned both *groEL/hsp60* and *rpoB* primer-less sequences (GenBank accession numbers: MH230168 and MH230167, respectively) close to *B. alsatica*. The identification was confirmed by *gltA* sequence analysis (GenBank accession numbers: MH230169) that presented 100% identity in a 337-nucleotide overlap using the NCBI Blast program. Accordingly, indirect immunofluorescence serological analyses (*Bartonella* IFA-Focus Diagnostics, Diasorin kit) were positive for *B. henselae* and *B. quintana* (IgG titer 1/1280 and 1/640, respectively, thresholds 1/320). Nevertheless, three different specific PCRs identified *B. alsatica*. We performed Western blotting using *Bartonella* sp. antigens, and after adsorption, the result was inconclusive, despite a slightly higher reactivity for *B. alsatica*.[7]

The antibiotic therapy was switched to 100 mg of doxycycline twice a day, resulting in a rapid drop in the fever and improvement of biological signs of inflammation. PET/CT re-evaluation after a 6-month doxycycline treatment showed a non-specific hypermetabolism of the new graft. Renal function significantly improved with time (serum creatinine 1.7mg/dL, urine protein-creatinine ratio 1g/g in January 2018). Accordingly, the PVGI was considered to be cured and doxycycline treatment was stopped.

## Discussion

The *Bartonella* genus was first described during World War I, since *B. quintana* was responsible for the trench fever which killed more than one million troops.[1] The bacterium *Rickettsia quintana* was isolated in the 1920s, cultured in the 1960s and reclassified as *B. quintana*. Thirty-five species have been identified so far but only 13 have been implicated in human infections.[1] Besides trench fever, *B. quintana* can be responsible for bacteremia, blood-culture-negative endocarditis, bacillary angiomatosis, bacillary peliosis, splenitis, osteomyelitis or orthopedic prosthesis infections, and chronic lymphadenopathy. *B. henselae* is also frequently involved in human infections and can be responsible for all the infections mentioned above, especially subacute lymphadenopathy and blood-culture-negative endocarditis.[1] Membranoproliferative glomerulonephritis has already been described in *B. henselae* infections,[8] however, it has never been associated with *B. alsatica* infection.

*Bartonella* spp. live in the gut of bloodsucking arthropod vectors (fleas, lice, ticks, and sandflies) and in the bloodstream of their mammalian hosts. The most well-known animal reservoirs are cats, rodents, and humans. However, new hosts have been identified such as marine mammals, camels, lions, bears, rabbits and foxes.[1]

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*B. alsatica* was first isolated from the blood of wild rabbits in Alsace, France, in 1999.[2] It is recognized as a wild rabbit pathogen causing bacteremia. Humans may be infected when they come into contact with wild rabbits while hunting, especially during evisceration with bare hands. They could also be infected by flea or tick bites.[2]

The present patient used to hunt wild rabbits regularly until 2015 and may have been infected at least two years before presentation of any symptoms. However, he never butchered the rabbits. Since 2015, he had only been hunting large wild game such as boars. He would still occasionally eat rabbit meat and had no recollection of ever being bitten by a tick. His wife, who butchered the rabbits, was not infected, suggesting that *B. alsatica* may present a tropism for patients with cardiovascular abnormalities including prosthetic grafts. This is in agreement with one of the two previously described *B. alsatica* endocarditis cases in which a bioprosthetic aortic valve was also infected.[4]

Laboratory diagnosis of Bartonella infections is difficult.[1] As *Bartonella* spp. are fastidious bacteria, blood and tissue culture have a low sensitivity (20–30%). Serological assays are widely used, especially indirect fluorescent antibody assays. However, the diagnosis at the species level is not reliable as there are a lot of cross-reactivities between *B. henselae, B. quintana* and other *Bartonella* species. Enzyme-linked-immunosorbent-assay, cross-adsorption and Western blot may also be used. Furthermore, diagnosis can be made by histopathology. Warthin-Starry silver staining can reveal dark-stained rods in various tissues, but immunohistochemical staining seems to be more specific. Molecular-based methods are now widely used, especially on various tissues (ie valvular, liver, etc) or grafts (ie valvular, vascular or orthopedic), as well as on whole blood, plasma or serum. Real-time PCR sensitivity is much higher than culture and more than specific than serology, especially for the diagnosis of *Bartonella* species. The most common molecular targets are the citrate synthase gene (*gltA*) and the RNA polymerase b-subunit gene (*rpoB*). However, the 16S rRNA gene-based PCR can also be useful and enables the microbiological diagnosis. Specific *B. alsatica* PCRs targeting *rpoB, gltA* and *groEL/hsp60* genes were also positive on samples of the patient's vascular graft.[1]

*Bartonella* spp. are difficult-to-treat bacteria due to their capacity to evade the host immune system, in particular by living within the erythrocytes, and their capacity to form biofilm. Therefore, infection relapses are frequent after antibiotic withdrawal. *Bartonella* spp. are susceptible to most beta-lactams (apart from oxacillin and cephalothin), aminoglycosides, macrolides, doxycycline, quinolones and rifampin. However, only gentamicin and, perhaps to a lesser extent, rifampin are bactericidal against *Bartonella* spp. Bartonella infection therapy depends on the type of infection. For instance, lymphadenitis can be treated by macrolides, eg azithromycin for 5 days only, but for endocarditis a combination of two antibiotic treatments are recommended, doxycycline for four weeks and gentamicin for two weeks.[1,9] Because there is no clear therapeutic recommendation for PVGI due to *Bartonella* spp., we successfully treated the patient with a long-course of doxycycline only. Gentamicin was not used due to the patient's acute renal failure.

In conclusion, the possibility of a *Bartonella* species infection should be considered in culture-negative cases of PVGI, as is currently done in blood culture-negative endocarditis. This case highlights the contribution of serology assays for PVGI diagnosis, especially targeting fastidious bacteria including *Coxiella burnetii, Bartonella* and *Brucella* species. However, molecular-based methods are helpful to elucidate and confirm diagnosis of these severe infections at the species level.

## Consent

Written informed consent was obtained from the patient for publication of this case report.

## Acknowledgment

Charles Cazanave and Sabine Pereyre equally contributed to this study.

## Disclosure

The authors report no conflicts of interest in this work.

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