Case Report

Bartonella henselae infection in a man with hypergammaglobulinaemia, splenomegaly and polyclonal plasmacytosis

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Bartonella henselae is an infrequently reported cause of polyclonal plasmacytosis and hypergammaglobulinaemia. We herein document B. henselae infection in a 66-year-old patient who presented with hypergammaglobulinaemia, splenomegaly with polyclonal plasmacytosis, stroke, and suspected prosthetic aortic arch infection. Clinicians should remain cognizant of the heterogeneous clinical presentations associated with bartonellosis.

Introduction

Bartonella species are fastidious Gram-negative, arthropod-transmitted bacteria that are capable of causing long-lasting intraerythrocytic bacteraemia in mammals. Frequently reported disease manifestations include non-specific malaise, adenitis, endocarditis and vasoproliferative lesions. As confirmation of Bartonella species infection by culture is the exception rather than the rule, serology, pathology and PCR amplification of organism-specific DNA sequences can facilitate diagnosis (Versalovic et al., 2011). The combination of hypergammaglobulinaemia, splenomegaly and polyclonal plasmacytosis is not known to have been reported in a human patient infected with a Bartonella species. Herein, we report a patient infected with Bartonella henselae that experienced hypergammaglobulinaemia, splenomegaly with polyclonal plasmacytosis, stroke and suspected infection of an aortic arch graft.

Case report

A retired 66-year-old male crop farmer had a history of atrial fibrillation, and placement of a coronary artery bypass graft, Dacron aortic arch graft and bioprosthetic aortic valve. He resided in a semi-rural area of North Carolina and had contact with outdoor cats. In July 2010, he reported persistent malaise, fatigue, low-grade fever and myalgia. Erythrocyte sedimentation rate was 84 mm h⁻¹; differential blood cell counts and a transthoracic echocardiogram were normal. A complete haemogram was unremarkable. Automated blood cultures (six sets obtained on three occasions) were negative. In September 2010, a temporal artery biopsy and rheumatologic evaluation were unrevealing, yielding a potential diagnosis of polymyalgia rheumatica. Antinuclear antibody by immunofluorescent antibody testing was negative, anti-Sjögren’s syndrome A (anti-SSA) antibodies were positive at a level of >8.0 antibody index units, with no clinical evidence of Sjögren’s syndrome. A magnetic resonance imaging (MRI) scan defined only age-related atrophy. Prednisone therapy was begun at 60 mg daily and then tapered to 10 mg daily after 2 months, eliciting transient improvement. However, there was then an indolent decline in functional status. In February 2011, the patient reported confusion and worsening cognition. He was thrombocytopenic (138 000 µl), hyperproteinemic (9.0 g dl⁻¹) and hypergammaglobulinaemic (IgG 5065 µg dl⁻¹; reference range 700–1600), with a polyclonal gammopathy. The spleen was palpable and abdominal computerized tomography (CT) identified marked, homogeneous splenic enlargement (Fig. 1a). Cytopathology of a bone marrow specimen revealed mild hypercellularity with polypytic plasmacytosis (10 %), and no immunophenotypic or cytogenetic abnormalities. In April 2011, a positron emission tomography (PET) scan identified increased metabolic activity in the spleen and ascending aorta (Fig. 1b, c). As lymphoma was suspected, splenectomy was performed. Grossly the spleen contained small infarcts. Histopathology revealed prominent polyclonal plasmacytosis with normal B cell immunophenotype (Fig. 1d). During post operative days (POD) 5–17, the patient developed a

Abbreviations: anti-SSA, anti-Sjögren’s syndrome A; PET, positron emission tomography; POD, post operative day(s).
right middle cerebral artery infarct, subsequently with left basal ganglia and focal occipital haemorrhage. During the post operative course, he developed intermittent fever and confusion. Automated blood cultures were again negative and no vegetations were observed by transthoracic echocardiogram. Due to suspected prosthetic aortic arch graft infection, fastidious bacteria that have been associated with culture-negative endocarditis became a diagnostic consideration. The patient’s *B. henselae* and *Bartonella quintana* IgG titres (ARUP Laboratories) were 1:2048 and 1:128, respectively. On POD 28, stored formalin-fixed and paraffin-embedded splenic tissues were submitted to the Intracellular Pathogens Research Laboratory, North Carolina State University, for *Bartonella* species PCR. Previously, we described *Bartonella* spp. DNA carryover during animal necropsy, and during the subsequent processing of tissue samples (Varanat et al., 2009a). Hence, special precautions are routinely taken in our laboratory when sampling paraffin blocks to minimize the DNA cross-contamination. Using a sterile scalpel, multiple sections were sliced from formalin-fixed and from paraffin-embedded splenic tissues, after which DNA was extracted using a Qiagen DNeasy Blood and Tissue kit according to the manufacturer’s instructions. For each PCR, a negative control was processed to ensure that extraction buffers and reagents were not contaminated with *Bartonella* DNA. PCR amplification using broad-range 16S rDNA gene primers yielded negative results (Arosio et al., 2008). PCR targeting the 16S–23S rRNA intergenic spacer (ITS) region of the *Bartonella* genome was performed as previously described (Maggi et al., 2005). No amplicons were obtained from the splenic tissue maintained for 28 days in formalin, whereas *B. henselae* DNA was amplified and successfully sequenced from three of five paraffin-embedded splenic tissue sections (Fig. 2). Presumably, long-term fixation in formalin resulted in cross-linking and fragmentation of DNA, thereby interfering with PCR amplification as compared with the short duration of fixation prior to embedding of the splenic tissue in paraffin.

Beginning on POD 27, the patient was treated with doxycycline and gentamicin for 2 weeks, followed by doxycycline and rifampicin for several weeks. Due to an adverse rifampicin–warfarin interaction, rifampicin was discontinued and doxycycline monotherapy was continued for 5 months. Beginning on POD 157, oral azithromycin 250 mg once daily for 10 months was administered. Revision cardiac surgery was not pursued, taking into account the patient’s frailty and his wishes. Upon receiving antibiotics, he dramatically improved. At 8 months post-diagnosis, the *B. henselae* IgG titre had decreased to 1:128. The patient had improved remarkably, and oral azithromycin was continued. Despite administration of antibiotics for 1 year, mild headaches persisted. By June 2012, a repeat MRI was unremarkable; however, his *B. henselae* antibody titre had increased to 1:2048.

**Discussion**

Prior to splenectomy, this patient experienced a protracted illness and complex disease course that defied a definitive
Bartonella vinsonii a cat with multifocal osteomyelitis in association with spanning an 18-month time frame have been reported in globulinaemia and plasma cell infiltration of bone interpretations by veterinary pathologists, hypergamma-
association with patient, are not known to have been described before in infections (Krause et al., 2003). However, plasmacytosis in the bone marrow and the spleen, as documented in this patient in July 2010, and post-operatively in April 2011. Although they are very non-specific symptoms, malaise, fatigue, myalgia and neurocognitive abnormalities are often reported in patients with chronic Bartonella bacteraemia (Breitschwerdt et al., 2007, 2011).

The clinical association between polyclonal gammopathy and chronic infection with intracellular bacteria or protozoa is well established; however, determining the infectious cause of hypergammaglobulinaemia can be challenging in some patients. Although infrequently reported to date, monoclonal and biclonal gammopathies have been reported in association with B. henselae infections (Krause et al., 2003). However, plasmacytosis in the bone marrow and the spleen, as documented in this patient, are not known to have been described before in association with B. henselae infection. Based upon repeated interpretations by veterinary pathologists, hypergammaglobulinaemia and plasma cell infiltration of bone spanning an 18-month time frame have been reported in a cat with multifocal osteomyelitis in association with Bartonella vinsonii subspecies berkhoftii bacteraemia (Varanat et al., 2009b). Thus, infection with a Bartonella species should be included in the differential diagnostic consideration for patients with unexplained plasma cell infiltration, splenomegaly, hypergammaglobulinaemia and polyclonal or monoclonal gammopathy. The spleen is occasionally involved in Bartonella species infections. Typically, hypodense lesions are reported on radiographic imaging. When these areas are biopsied, one most commonly encounters necrotizing granulomas. In our patient, despite the lack of granulomatous inflammation, serology, PCR amplification and DNA sequencing results supported infection with B. henselae as a unifying diagnosis. In addition, splenic Bartonella infection has been reported in a patient following splenectomy performed for suspected malignancy (Ghez et al., 2001).

Based upon this patient’s symptoms and rheumatological testing, including a positive anti-SSA, prednisone was administered for several months prior to surgical intervention. The PET scan demonstrated increased metabolic activity in the ascending aorta, which in retrospect, potentially supported localization of B. henselae organisms to this anatomical location. Previous studies have identified pre-existing valvular disease as a risk factor for the development of B. henselae endocarditis (Fournier et al., 2010). In two earlier case reports, patients developed endocarditis after therapeutic immunosuppression was initiated based upon positive anti-neutrophil antibody tests (Turner et al., 2005). Similarly, B. vinsonii subspecies berkhoftii genotype I endocarditis was reported in a dog from North Carolina after therapeutic immunosuppression was initiated for suspected systemic lupus erythematosus, based upon positive anti-nuclear antibody reactivity (Breitschwerdt et al., 1995). Thus, it is possible that immunosuppression may facilitate B. henselae localization to heart valves or to prosthetic implants, and based upon the patient’s most recent B. henselae titre, antibiotic elimination of these bacteria may be difficult to achieve. Based upon multiple patient management factors, cardiac revision surgery was not performed to address a potentially infected bioprosthetic aortic valve or Dacron aortic arch implant.

Based upon recent research observations, infections with Bartonella species represent a previously unrecognized cause of persistent bacteraemia in immunocompetent patients. Infection with a spectrum of Bartonella species is an important diagnostic consideration in patients with culture-negative endocarditis and is also occasionally encountered in patients with prosthetic valve endocarditis.

**Conclusion**

Based upon this case report, bartonellosis should be considered in patients with unexplained fatigue, myalgia, neurocognitive abnormalities, splenomegaly, hypergammaglobulinaemia and splenic or bone marrow plasmacytosis. Clinicians should consider bartonellosis as a
differential diagnosis in an expanding number of clinical scenarios.

References


