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Prostatitis, Steatitis, and Diarrhea in a Dog following Presumptive Flea-Borne Transmission of *Bartonella henselae*

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Bartonella henselae **is increasingly associated with a variety of pathological entities, which are often similar in dogs and human patients. Following an acute flea infestation, a dog developed an unusual clinical presentation for canine bartonellosis. Comprehensive medical, microbiological, and surgical interventions were required for diagnosis and to achieve a full recovery.**

CASE REPORT

On 18 July 2012, a 6-year-old, 29.1-kg intact male Irish setter was referred to the North Carolina State University College of Veterinary Medicine, Veterinary Health Complex (NCSU-CVM-VHC), for evaluation of a 6-week history of chronic large bowel diarrhea, intermittent vomiting, and tenesmus. The owners reported that the onset of clinical signs began shortly after oral treatment for a severe flea infestation, acquired 6 weeks earlier during a beach vacation in the southeastern United States. Subsequently, the dog became progressively lethargic, had lost approximately 5.5 kg despite a normal to slightly reduced appetite, was reluctant to climb stairs or participate in normal exercise, and appeared to have abdominal pain. When evaluated by the referring veterinarian on 27 June 2012, complete blood count (CBC) results were consistent with a stress leukogram. Serum biochemistry panel, trypsin-like immunoreactivity, and vitamin B_{12} and folate levels were within normal limits. Fecal flotation was negative for parasites or ova. A normal adrenocorticotropic hormone (ACTH) stimulation assay ruled out hypoadrenocorticism. An abdominal ultrasound revealed diffuse thickening of the intestinal wall. The dog had been treated empirically for 5 days with metronidazole (8.6 mg/kg of body weight orally [p.o.] every 12 h [q12h]), sucralfate (1 g p.o. q8h), omeprazole (0.7 mg/kg p.o. q24h), amoxicillin (17.2 mg/kg p.o. q12h), and tramadol (1.7 mg/kg p.o. q8h to q12h).

At referral to NCSU-CVM-VHC, the dog was bright, alert, and well hydrated. Physical examination abnormalities included poorly localized pain, including the dorsal lumbosacral region, and pain elicited during tail extension and rectal examination. Live fleas were noted. Radiographs identified lateralized spondylosis deformans involving the lumbosacral vertebrae. Thoracic radiographs were normal. Abdominal ultrasonographic examination changes, limited to the caudal abdomen, included an amorphous hypoechoic left caudal abdominal mass and mild right medial iliac and jejunal lymphoadenomegaly. Fine-needle aspiration (FNA) specimens from the ill-defined abdominal mass revealed moderate to marked suppurative inflammation with 93% nondegenerate neutrophils. No organisms were visualized. Prostatic wash cytology was consistent with epithelial dysplasia and squamous metaplasia. CBC abnormalities included neutrophilia ($9.9 \times 10^3/\mu l$, reference interval [RI] of $2.8 \times 10^3/\mu l$ to $9.1 \times 10^3/\mu l$) with 230 band neutrophils/μl and lymphopenia ($0.239 \times 10^3/\mu l$, RI of $0.594 \times 10^3/\mu l$ to $3.305 \times 10^3/\mu l$). Serum biochemistry values were within RIs, except for creatinine (0.6 mg/dl, RI of 0.7 to 1.5 mg/dl). Urinalysis revealed proteinuria (1+) and hyperbilirubinuria (3+), with urine specific gravity of 1.040. Urine culture did not grow bacteria. To better delineate caudal abdominal anatomy, a contrast computerized tomography (CCT) scan revealed a markedly enlarged prostate (38 mm) with heterogeneous parenchyma, multiple small cysts, and amorphous mineralization of the left lobe (Table 1). The prostate was caudally located, and there were several fluid-filled pockets caudal to the prostate consistent with bilateral perineal hernia. Wisps of soft tissue attenuation throughout the mesentery and periprostatic fatty tissue supported caudal abdominal inflammation consistent with steatitis with no discrete mass.

Based upon historical disease onset following a severe flea infestation, canine vector-borne disease (CVBD) serology and *Bartonella* alpha *Proteobacteria* growth medium (BAPGM) enrichment blood culture were performed as previously described (1). By immunofluorescence assay (IFA) and SNAP 4Dx enzyme-linked immunosorbent assay (ELISA; IDEXX Laboratories, Westbrook, ME), the dog was not reactive against *Anaplasma* spp., *Babesia canis*, *Borrelia burgdorferi*, *Bartonella henselae*, *Bartonella vinsonii* subsp. *berkhoffii*, or *Ehrlichia canis*, whereas the *Rickettsia rickettsii* IFA antibody titer was 1:64. The *Dirofilaria immitis* antigen assay was also negative. By targeting the *Bartonella* 16S-23S intergenic transcribed spacer (ITS) region, as previously described (1), *Bartonella henselae* San Antonio 2 (*Bh*SA2) DNA was PCR amplified and sequenced from blood, whereas BAPGM enrichment blood cultures on 7, 14, and 21 days were PCR negative (Table 1). Simultaneously, the BAPGM broth was subcultured onto tryptic soy agar II (TSA) supplemented with 5% rabbit blood (Becton, Dickinson Diagnostic Systems, Sparks, MD). The plates

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TABLE 1 Diagnostic test results obtained prior to and after directed antibiotic (ciprofloxacin and doxycycline) treatment for canine bartonellosis[d]

Diagnostic period	Mo and yr of evaluation	*Bartonella* 16S-23S intergenic element PCR result			*Bartonella henselae* serology (IFA) titer	SNAP 4Dx ELISA result[c]	*Rickettsia* serology (IFA) titer	*Rickettsia* PCR result from blood	Prostrate dimension (mm) by CT or abdominal ultrasound
		PCR from blood	PCR from BAPGM enrichment culture	*Bartonella* PCR from prostate tissue					
Initial	July 2012	*Bh*SA2 positive	Negative for *Bartonella* spp.	*Bh*SA2[a] positive	<1:16	Negative	1:64	Negative for *Rickettsia* spp.	38
Posttreatment	November 2012	Negative for *Bartonella* spp.	Negative for *Bartonella* spp.	NA	<1:16	ND	1:64	Negative for *Rickettsia* spp.	11.3
	December 2012	ND	ND	Negative[b] for *Bartonella* spp.	ND	ND	ND	Negative for *Rickettsia* spp.	14.5
	January 2013	Negative for *Bartonella* spp.	Negative for *Bartonella* spp.	NA	<1:16	Negative	1:16	Negative for *Rickettsia* spp.	16

[a] Formalin-fixed paraffin-embedded prostrate tissue.
[b] Surgically excised fresh prostrate tissue.
[c] IDEXX Laboratories, Westbrook, ME.
[d] *Bh*SA2, *Bartonella henselae* San Antonio 2; IFA, microimmunofluorescence assay; ND, not done; NA, not applicable, no prostatic tissue obtained. <1:16 was considered nonseroreactive.

were incubated at 35°C containing 5% CO_2 and 99% relative humidity for 6 weeks. The subcultures were PCR negative for *Bartonella*. The dog was discharged with instructions for administration with enrofloxacin (10 mg/kg p.o. q24h), doxycycline (5 mg/kg p.o. q12h), omeprazole (0.75 mg/kg p.o. q24h), tramadol (3 mg/kg p.o. q8h to q12h), and sucralfate (1 g p.o. q8h).

Seven days later, the dog was rehospitalized at NCSU-CVM-VHC due to continued lethargy and reluctance to climb stairs, soft stools several times/day, and tenesmus. Body weight had decreased an additional 1.5 kg. CBC abnormalities included increased segmented neutrophils (10,060/μl), with no band neutrophils or toxic changes, lymphopenia (121/μl, RI of 594 to 3305/μl), and monocytosis (1,697/μl, RI of 0.075 to 850/μl). Serum creatinine (0.5 mg/dl) was again below the RI, whereas other chemistry values were again within RIs. Coagulation profile values were within RIs. Abdominal ultrasound and fluid analysis were consistent with prostatitis, regional peritonitis, and peripelvic inflammation. Abdominal fluid analysis revealed 51,190 nucleated cells/μl, predominantly comprised of nondegenerate neutrophils, moderate numbers of reactive mesothelial cells, occasional dysplastic mesothelial cells, a few foamy macrophages, protein of 3.8 g/dl by refractive index, and specific gravity of 1.025. Colonic cytology identified a marked proliferation of atypical mesenchymal cells. Prostatic cytology identified moderate numbers of elongated to spindle-shaped cells containing one to multiple nucleoli and occasional multinucleated cells. Analysis of prostatic cyst fluid revealed 630 nucleated cells/μl (5% nonregenerative neutrophils, 80% small mononuclear cells, 12% large mononuclear cells, and 3% plasma cells), protein of 2.7 g/dl, and specific gravity of 1.020. On exploratory laparotomy, the distal descending colon contained multiple, 1- to 2-mm raised, red, firm nodules and plaques. Colonic lesions were surgically excised; the jejunum, duodenum, rectum, prostate, and colonic lymph node were also biopsied, and the dog was castrated. Postoperative recovery was uneventful.

Postsurgically, the dog received intravenous (i.v.) fluids, ampicillin-sulbactam (22 mg/kg i.v. q8h), and analgesics. Concurrently, amikacin (15 mg/kg i.v. q24h for 7 days), ciprofloxacin (28.5 mg/kg p.o. q24h), and doxycycline (5.7 mg/kg p.o. q12h) were also administered for treatment of bartonellosis. The dog was discharged with instructions for administration of ciprofloxacin (28.5 mg/kg p.o. q24h), omeprazole (0.75 mg/kg p.o. q24h), tramadol (2 to 4 mg/kg p.o. q8h to q12h), amoxicillin-clavulanate (16.6 mg/kg p.o. q12h), doxycycline (5.7 mg/kg p.o. q12h), and gabapentin (7.6 mg/kg p.o. q12h).

Aerobic and anaerobic cultures of surgically excised peritoneum and colonic lesions were negative for bacterial or fungal growth. By histopathology, the colonic lesions contained well-organized granulation tissue, edema, and mild hemorrhage and fibrin deposition, with reactive mesothelial cells, admixed with small to moderate numbers of degenerate and nondegenerate neutrophils. Histopathologically, there was mild eosinophilic enteritis of the duodenum, jejunum, and ileum. The prostate was infiltrated with neutrophils, lymphocytes, and plasma cells, admixed among a presumptive neoplastic infiltrate composed of plump spindle to epithelioid cells. By immunohistochemistry (IHC), the prostate contained diffuse, cytoplasmic vimentin immunoreactivity and strong cytoplasmic cytokeratin immunoreactivity. The prostate was negative for factor VIII, thereby ruling out hemangiosarcoma. The colonic lymph node contained numerous hemosiderin-laden macrophages, indicative of draining hemor-

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rhage. Warthin-Starry staining of the colon and prostate did not identify an infectious agent.

Formalin-fixed paraffin-embedded duodenum, colon, colonic lymph node, and prostatic tissues were submitted to the North Carolina State University Intracellular Pathogens Research Laboratory (NCSU-IPRL) for *Bartonella* PCR. As described previously, special precautions were taken when sampling paraffin blocks to prevent DNA cross-contamination (2). *Bh*SA2 DNA was PCR amplified and successfully sequenced from paraffin-embedded prostate. *Bartonella* ITS PCR of the duodenum, colon, and colonic lymph node was negative. *Bartonella* confocal microscopy was performed at the University of Minnesota Imaging Center (UMIC) from the paraffin-embedded prostate tissue using a previously described procedure (3). Duplicate prostate sections were incubated without antibodies to account for nonspecific binding. *Bartonella* spp.-negative dog and human skin was used as a negative control. Neither controls displayed *B. henselae* immunoreactivity. Confocal imaging revealed immunoreactive *B. henselae* in the dog prostatic tissue (Fig. 1a to d).

When the dog was reexamined on 6 September 2012, the owners reported substantial improvement in attitude and activity; however, occasional soft stools persisted. Physical examination was unremarkable. The dog had gained 3.4 kg. By abdominal ultrasound, the prostate was more symmetric and reduced in size (23.4 mm) compared with results from the initial evaluation (38 mm). The dog was discharged with instructions for the owners to continue giving ciprofloxacin and doxycycline as previously directed until 13 October 2012, when antibiotics were discontinued. When the dog was reevaluated on 8 November 2012, the owners reported that the dog had returned to a normal state of health. Physical examination, CBC, and a serum biochemical profile were unremarkable. By abdominal ultrasound, the prostate was further reduced in size (11.3 mm); however, there were new small parenchymal cysts and three periprostatic fluid pockets. By FNA, the cystic fluid contained rare foamy macrophages. Aerobic and anaerobic cystic fluid cultures were negative for bacterial and fungal growth, but fluid was not submitted for *Bartonella* PCR.

On 11 December 2012, the owners reported intermittent straining during urination. By rectal examination, there were bilateral perineal hernias. Abdominal ultrasound documented position-dependent herniation of the prostate and urinary bladder. The prostate was slightly larger (14.5 mm) and more heterogeneously echogenic. Concurrently, the hernia was surgically corrected and the prostate biopsied. There was no histopathological evidence of neoplasia, inflammation, or cystic changes within the prostate biopsy specimen. *Bartonella* serology was negative, whereas the *R. rickettsii* antibody titer was 1:64. Posttreatment blood, prostate, and BAPGM enrichment blood and prostate cultures were *Bartonella* PCR negative. At follow-up on 25 January 2013, there was no antibody reactivity to any *Bartonella* sp. antigen, BAPGM enrichment blood culture/PCR results were again negative, and the *R. rickettsii* titer was 1:16. The dog remained healthy through April 2014.

This dog's 6-week history of chronic large bowel diarrhea, accompanied by weight loss, intermittent vomiting, and tenesmus, prompted his owners to seek referral to the NCSU-VHC. While baseline clinicopathological results were nonspecific or largely unremarkable, advanced imaging and histopathology findings were suggestive of prostatic disease with regional abdominal inflammation and steatitis secondary to either infection or neoplasia. Because this previously healthy dog had a sudden onset of illness following vacation exposure to fleas, infection with a flea-transmitted pathogen, such as *B. henselae*, became a diagnostic consideration. Although the owners did not report previous flea infestations, it is impossible to determine when or how this dog became infected with *B. henselae*. Postoperatively, when special stains applied to the prostatic biopsy sections were inconclusive for neoplasia and urine and tissue bacterial and fungal cultures were negative, prostatitis secondary to a fastidious infectious agent became a more focused diagnostic consideration. In conjunction with confocal immunohistochemical visualization of *B. henselae*, PCR amplification and sequencing of the same *B. henselae* ITS genotype (SA2) from blood and subsequently from the paraffin-embedded prostate biopsy specimen supported a contributing or causative role for this bacterium in the dog's prostatic pathology. Progressive improvement following *B. henselae*-directed antibiotic therapy (4) lent further support for a diagnosis of canine bartonellosis. Finally, negative postantibiotic *B. henselae* PCR results from enrichment blood and prostatic biopsy BAPGM cultures, obtained at the time of hernia repair, supported therapeutic elimination of *B. henselae*.

Given that *Bartonella* infections appear to manifest in highly varied disease states, a concise diagnostic algorithm does not exist; however, this dog had several findings suggestive of bartonellosis. In a case-control study, weight loss was significantly associated with *Bartonella* infections in dogs (5). Although anemia, thrombocytopenia, thrombocytosis, eosinophilia, and monocytosis (this dog) occur in association with canine bartonellosis, a lack of hematological and biochemical changes is not unusual, despite a severe progressive course of illness (5, 6). As diarrhea has not been reported as a distinct clinical entity in dogs infected with *Bartonella* spp., the colonic diarrhea, eosinophilic enteritis, and weight loss in this dog may have been secondary to the regional abdominal inflammation or another undetermined infectious or noninfectious cause. However, on a comparative microbiological basis, *B. henselae* has been associated with ileitis and inflammatory bowel disease in a 13-year-old boy (7) and colitis in a human patient with *B. henselae* endocarditis (8). Thus, future consideration should be given to *B. henselae* infection among other differential diagnoses in dogs and human patients with diarrhea. Steatitis, suspected from the abdominal CT scan and confirmed histologically, lent further support for a possible infectious/inflammatory etiology. As cutaneous panniculitis (inflammation of the panniculus adiposus) has been associated with *B. henselae* infections in dogs and human patients (4, 9–11), the possibility that steatitis (analogous inflammation of adipose tissue in the abdomen) was induced by *Bartonella* infection in this dog seemed plausible.

For reasons that remain incompletely understood, approximately three quarters of *B. henselae*-infected dogs (PCR positive from blood, tissues, or BAPGM enrichment blood or tissue culture) do not have detectable *B. henselae* antibodies by IFA testing (5, 12, 13). Therefore, IFA serological diagnosis of bartonellosis currently lacks sensitivity, for reasons that in part remain unclear. This dog was *B. henselae* seronegative prior to and after antibiotic therapy. Similar discrepancies between serology and PCR results have been reported in association with other chronic, occult, intracellular canine vector-borne diseases, including babesiosis and leishmaniasis (14, 15). Also, this dog, similar to a subset of *B. henselae*-infected dogs, was *R. rickettsii* seroreactive, potentially

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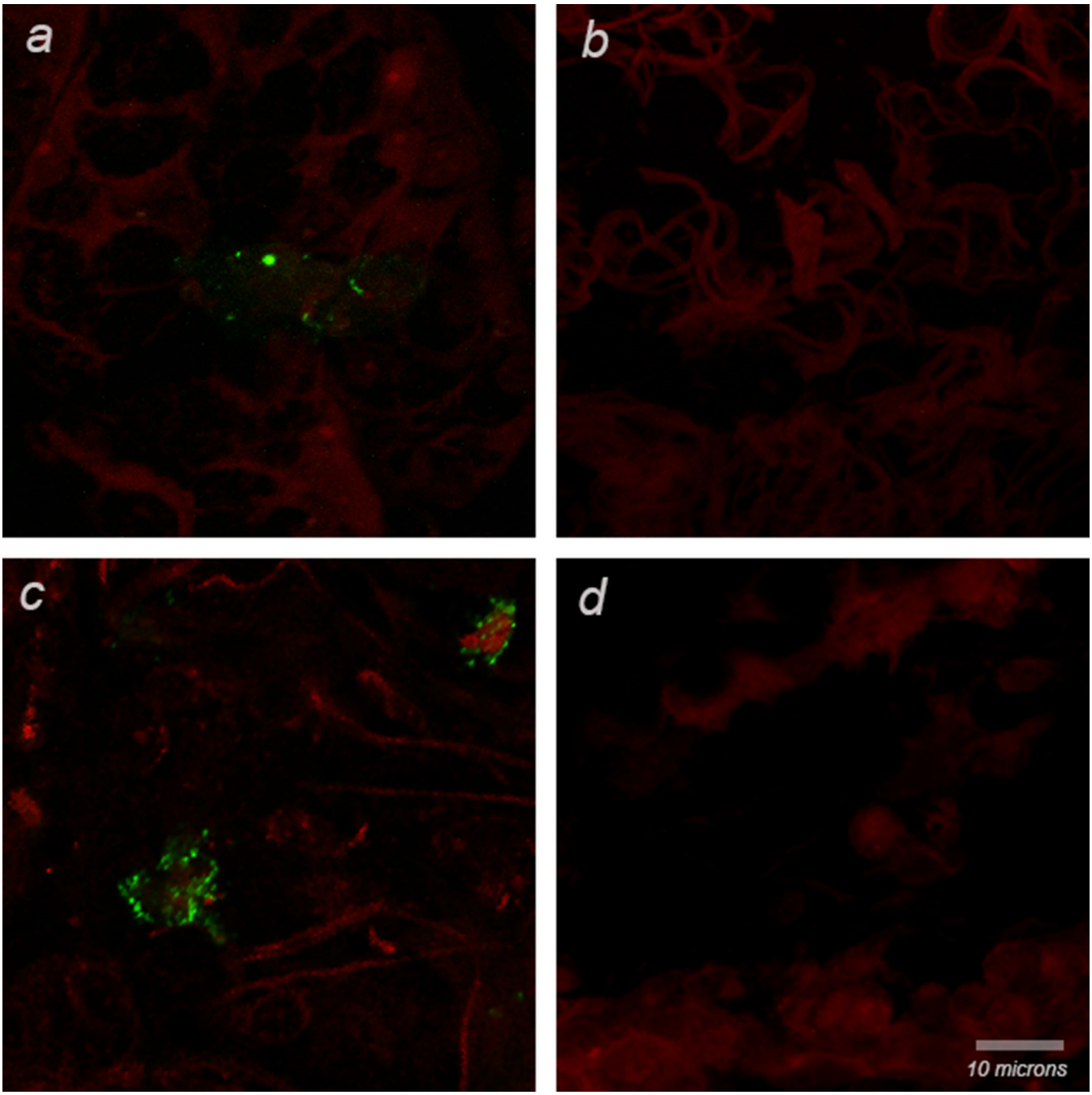

FIG 1 Confocal microscopy demonstrates *Bartonella henselae* immunoreactivity (green color) in dog prostate tissue (A), secondary antibody negative control (dog prostate tissue) (B), positive control (human skin tissue with *Bartonella henselae*; green color) (C), and negative control (noninfected human skin tissue) (D).

due to concurrent exposure to flea-transmitted *Rickettsia felis* (13). Retrospective efforts to PCR amplify *Rickettsia* spp. DNA from the dog's stored blood specimens were not successful. Based upon currently available microbiological techniques, diagnostic confirmation of *Bartonella* infection can be achieved by culturing the organism or by amplifying organism-specific DNA sequences from aseptically obtained blood, effusions, exudates, and tissues prior to or following BAPGM or other enrichment culture approaches (4, 16, 17). Despite PCR amplification of *Bh*SA2 DNA from the dog's blood, BAPGM enrichment blood culture failed to support organism growth, which can occur due to a low bacterial inoculum, due to a lack of viable bacteria in the cultured blood sample, or due to other unknown factors that adversely influence the growth of these bacteria. Administration of amoxicillin and metronidazole immediately prior to obtaining blood for BAPGM enrichment blood culture may have inhibited bacterial growth.

While *Bartonella* spp. have a tropism for endothelial cells and erythrocytes, these bacteria are able to invade other nucleated cells

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(pericytes, dendritic cells, monocytes, and microglial cells) using specific outer membrane adhesion proteins and integrins (18, 19). *Bartonella* spp. DNA has been amplified from numerous canine tissues, particularly in association with granulomatous inflammation (4). Based upon current understanding, PCR often successfully amplifies organism-specific DNA sequences from heavily infected tissues, particularly in immunocompromised individuals or in patients with acute *Bartonella* infections (2). However, although successful in specific instances, PCR amplification of *Bartonella* spp. DNA from patients with chronic intravascular infections or patients with localized parenchymal tissue involvement of the liver, spleen, and kidney, which can contain low numbers of bacteria, is less sensitive (20, 21). From a clinical or pathological perspective, it is important to realize that failure to amplify *B. henselae* DNA from this dog's intestinal and colonic biopsy specimens does not confirm that the bacteria did not infect these tissues, particularly as bloodstream infection was implicated simultaneously by PCR. Similarly, PCR amplification of *B. henselae* DNA from blood and prostate does not confirm that this bacterium was the sole cause of the dog's illness or the histologically documented pathology found in various tissues. The most common conditions affecting canine prostate includes benign prostatic hyperplasia, bacterial prostatitis, prostatic cysts, and neoplasia (22). The most common bacterial cause of canine prostatitis is *Escherichia coli*, although many other bacterial organisms have been reported (22). Based on overlapping clinical signs, an empirical diagnosis of infectious prostatitis and neoplasia was initially considered most likely in this dog. Due to the poor prognosis (23) for prostatic neoplasia in comparison with bacterial prostatitis in dogs, the diagnostic differentiation was critical. Because intestinal biopsy specimens from this dog identified mild inflammation, a separate disease process involving the gastrointestinal tract was also considered likely, including parasitic infection, eosinophilic gastroenteritis, or neoplasia; however, neither our test results nor the response to therapy supported these entities as concurrent diseases.

Although cats are considered the primary reservoir host, *B. henselae* DNA has been PCR amplified from cows, dogs, horses, feral swine, marine mammals, and sea turtles (4, 12). Similarly, although cat fleas (*Ctenocephalides felis*) are considered the primary vector for transmission to reservoir and potentially nonreservoir hosts, such as dogs and humans, *B. henselae* DNA has also been amplified from *Ixodes* ticks (24), woodlouse hunter spiders (25), and most recently tropical rat mites (26). Based upon the dog's medical history, flea infestation while on vacation was the presumed source of infection. Assuming this mode of transmission, exposure to fleas resulted in a persistent *B. henselae* infection that precipitated a diagnostically challenging disease process, two major surgical interventions, substantial medical care, a long-duration antibiotic regimen, and medical and surgical costs in excess of $15,000. Historically, *C. felis* was considered a relatively benign ectoparasite that induced itching and flea allergy dermatitis in dogs and was responsible for intestinal *Dipylidium caninum* infections. An emerging paradigm indicates that *C. felis* and other arthropod vectors are responsible for the transmission of several *Bartonella* spp. to animals and humans throughout much of the world (4, 27). Therefore, it is important for physicians and veterinarians to clarify whether exposures to fleas, particularly the highly prevalent "cat flea" that also infests dogs, has occurred when obtaining the medical history from an animal or human patient.

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In conjunction with Sushama Sontakke and North Carolina State University, E. B. Breitschwerdt holds U.S. patent no. 7,115,385, "Media and methods for cultivation of microorganisms," which was issued 3 October 2006. He is the chief scientific officer for Galaxy Diagnostics, a company that provides advanced diagnostic testing for the detection of *Bartonella* species infection in animals and humans. Other authors have no competing interests.

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