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NEWSLETTER

Feline *Bartonella* Diseases: Cat Got Your Spleen?

Evelyn E. Zuckerman, Editor **Winter 2020** **Vol. 19, Number 1**

In This Issue:

The Winter 2020 issue of the NVL Newsletter will discuss the spectrum of feline *Bartonella* species diseases of the spleens in cats, dogs and zoonotically in people. To "vent one's spleen" is to let out anger. The cat got your spleen? We ask this because feline derived *Bartonellae* can affect the spleens of cats, dogs and especially people due to the spleen's unique functions.

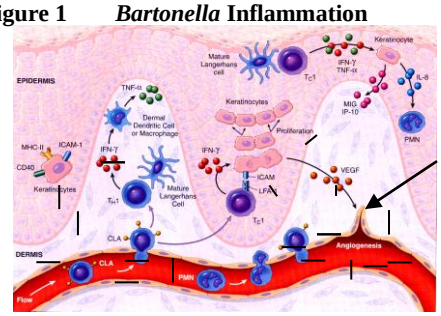
The Spleen:

The spleen is a highly vascular component of the immune system. It filters out senescent red blood cells in the red pulp and stores a large reserve for RBCs, if needed in blood loss. The white pulp has a reserve of monocytes, and is a component of the active immune response by producing T and B lymphocytes for the cell-mediated and humoral immune pathways. Resident macrophages are very active in clearing blood borne viral, protozoan and bacterial pathogens, especially tick-borne agents.

Bartonella Pathogenesis

Feline *Bartonella* possess pili which are hair-like structures found on the bacteria's surface. *Bartonella* have a strong tendency to stick to, and penetrate, RBCs and endothelial cells. The ability to adhere to each other, and to the membranes of RBCs and endothelial cells, leads to the wide and varied tissue pathogenesis observed in cats, dogs and people.

Figure 1 *Bartonella* Inflammation



Legend: The black rods (--) represent *Bartonella* in the skin or mucosa. The bacteria induce angiogenesis (arrow) and an outpouring of inflammatory cytokines which recruit inflammatory cells such as lymphocytes, plasma cells and macrophages.

Since the spleen filters out damaged or modified RBCs and blood borne pathogens, it should be at high risk, in all animals, to the *Bartonella*-induced inflammatory pathogenesis. The wide tissue specificity of *Bartonella* (Figure 1) is due to the adhesion to endothelial cells which are the constituents of capillaries found in all tissues. *Bartonella* proteins stimulate endothelial cells to proliferate causing chronic lymphocytic granulomatous inflammation.[1]

Bartonellosis:

Bartonella Spleen Diseases:

Bartonellosis encompasses all *Bartonella* diseases, cat scratch disease (CSD) and atypical CSD. Bartonellosis is characterized by inflammation of vascularized tissues. Inflammatory reactions often occur concurrently in multiple sites such as lymphoid, ocular, and major organs. However, the spleen although highly susceptible, appears to be able to often escape *Bartonella* pathogenesis in most animals.

Cats:

Feline spleen diseases are not common in cats. During our 20 years of *Bartonella* testing, we tested 395,573 cats by our Fe*Bart*® *Bartonella* western blot (WB) and only 145 cats were submitted with a diagnosis of splenomegaly. Of these 145 cats, 57 (39.3%) were serologically positive.[2]

Dogs:

Similar to cats, dogs do not have many *Bartonella* diseases of the spleen. We tested 89 dogs with splenomegaly during our 20 years of testing and only 15 (16.9%) were seropositive. However, this prevalence was more than the overall dog prevalence of 4.5% (1,176 of 10,570).[2]

There are three reports of *Bartonella*-induced spleen diseases in dogs. Dog splenomegaly can be caused by 2 inflammatory conditions, lymphoid nodular hyperplasia (LNH), and fibrohistiocytic nodules (FHN) and neoplasia splenic hemangiosarcoma (HSA). The first study found that *Bartonella* sp. DNA was found in 29.7% of FHN and 26% HAS and 10% LNH, but none in control spleens.[3] The second more recent study reported not being able to find any *Bartonella* DNA in any spleens of 78 dogs with splenic diseases.[4] The most recent study found a high occurrence (73%) of *Bartonella* DNA in HAS tumors of dogs from throughout the USA.[5] There were 74 splenic HAS in the study and 24 (32%) had detectable *Bartonella* DNA. The remaining HASs were cardiac and other sites. No *Bartonella* DNA was found in the blood of the dogs with HAS and only 6% were seropositive by IFA. There was no control group for this retrospective study. Further studies are needed to determine the direct oncogenic contribution of *Bartonella* to neoplasia.

Human:

There are more publications of *Bartonella*-induced spleen diseases in humans than animals.

CSD and Atypical CSD:

All *Bartonella* diseases are not CSD. CSD is the prototypical *Bartonella* disease but, in fact, may only represent about 50% of the clinically evident *Bartonella* diseases. CSD is characterized by a prodrome (the earliest consistent sign of a disease) of fever (usually prolonged or intermittent), a papule at the scratch or bite site, and lymphadenopathy.

Most physicians and veterinarians are familiar with classical CSD signs, but are not as familiar with the sequelae that occur in atypical CSD. Sequelae are defined as conditions that follow as a consequence of a disease or infection and may remain long after the initiating disease or infection. CSD has many sequelae including neurologic inflammatory disease, psychotic and cognitive disorders, ocular, heart, musculoskeletal and major organ inflammatory conditions. Thus, CSD may be envisioned as only the tip of the "*Bartonella* disease iceberg."

A healthy person who becomes infected after contact with a cat may remain asymptomatic and his or her infection may resolve. However, an infected healthy person may become symptomatic within 1 to 6 weeks and develop classical CSD with fever, a papule and lymphadenopathy. CSD will resolve, without therapy, in 80% of people, however, about 20% will develop sequelae (atypical CSD) after the resolution of classic CSD. Some symptomatic patients develop classic CSD and sequelae at essentially the same time. Similarly, some infected asymptomatic individuals will develop only sequelae (atypical CSD) weeks after their infection. These individuals are difficult for physicians to diagnose since they present with symptoms different from classical CSD, such as prolonged fevers, abdominal pain and increased markers of chronic inflammation such as elevated erythrocyte sedimentation rate or C-reactive protein. Often there is no mention of cat contact in the patient's history. **These are the 3 main signs of atypical splenic CSD.**

Splenic *Bartonella* Diseases:

Atypical splenic CSD can occur in immunocompromised or immunocompetent children (80%) and adults (20%). It is the most difficult form of bartonellosis to diagnose and may rarely be fatal because of misdiagnosis. There is a rich literature on this subject.

Pediatric Splenic Atypical CSD:

Study 1: As was just noted, more cases of spleen involvement occur in children. Most reported cases involve both the spleen and liver but occasionally can also involve other organs such as the kidneys and vertebrae. A case occurred in an infant only 16 months old who had prolonged fever for 7 days and inguinal lymphadenopathy. Antibiotic therapy did not resolve the fever.[6] There was a history of cat contact and biopsy of the lymph node showed a positive silver stain, which was followed with a positive serology. The child was treated with azithromycin for 5 weeks and his fever quickly resolved while his splenic micro-abscesses resolved after 4 months.

Study 2: Another pediatric study of 19 cases reported the chief complaint to be prolonged fever lasting from 7 to 56 days (mean 22 days) and abdominal pain in 13 children.[7] All were seropositive for *Bartonella henselae* (*Bh*). Sixteen of the 19 children were treated with rifampin alone (13) and rifampin plus another antibiotic (3) for 21 days. Improvement was quickly noted in all cases in a mean of 2.6 days. The authors recommend rifampin therapy for hepatosplenic CSD.

Study 3: A study of 7 *Bh* seropositive cases with atypical hepatosplenic granulomata CSD had prolonged follow-ups. Macrolides (azithromycin) or a combination of 2 active antibiotics for 14 to 21 days led to definitive clearance of infection and rapid clinical improvements, although lesions persisted in 5 patients for several months or years.[8]

Study 4: In a study of 127 children with serologically positive CSD, 59.1% had classic CSD whereas 40.9% had atypical CSD.[9] Atypical CSD manifestations were prolonged fever and splenic abscesses or low-echoic spleen lesions.

Adult Splenic Atypical CSD:

As indicated before, 20% of atypical CSD cases occur in adults. The same triad of clinical signs suggest splenic involvement in the pathogenesis- 1) prolonged fever of unknown origin, 2) abdominal pain and 3) increased markers of chronic inflammation such as elevated erythrocyte sedimentation rate or C-reactive protein. Often there is no history of cat contact.

Study 5: An excellent detailed paper from Spain of 36 cases gives complete signalment, diagnostic criteria and detailed therapy of 3 new cases and a review of 33 additional atypical CSD cases.[10] A disturbing observation was the mean time to diagnoses, of 26 of the 36 cases (73%), being 7.78 weeks (range of 1-52 weeks). As a result of delayed diagnoses, a splenic rupture with hemoperitoneum, occurred in one of these cases requiring a splenectomy.[11] Almost all of these cases used positive *Bh* serology for diagnosis and excellent therapeutic results were reported.

Study 6: To illustrate the difficulty of diagnosing atypical CSD, a case of *Bartonella*-induced splenic rupture is a pertinent example.[11] A 63-year-old man developed massive hemoperitoneum secondary to rupture of his spleen. He had acute-onset abdominal pain without any history of trauma or fever. He had 5 cats at home including several kittens, but could not recall any recent bites or scratches. Initial tentative diagnosis by CT scan was secondary rupture of the splenic artery or rupture of an aortic aneurysm. At the time of admission he had a fever and diffuse abdominal tenderness. Exploratory laparotomy found free blood in the abdomen, a 4-cm tear in the spleen, and 3 firm masses in his spleen. The liver appeared normal and a splenectomy was performed. Histology showed multiple necrotizing granulomas and microabscesses.

Blood drawn 2 days after surgery showed no bacterial growth but the cultures were incubated for only 4 days. Due to the lack of suspicion of bartonellosis, 1 week after surgery, blood was drawn for general serology which showed high IgG *Bh* titer of ≥1:1,024, but <1:20 for IgM, indicating the chronic nature of his infection. He was treated with a 20-week course of oral doxycycline and he remained symptom free. A follow-up serological evaluation at 5 months post-therapy showed a reduction of the *Bh* titer to 1:32, a 32-fold or greater reduction from the pretherapy titer of ≥1:1,024.

Study 7: This is an example of a possible misdiagnosed case of atypical CSD which led to a more serious illness 4 years later. A 51-year old man with a history of undiagnosed pulmonary nodules, 4 years before, presented with right-sided chest pain.[12] A cardiac work-up was normal, but an abdominal computer tomography (CT) found small hypodense lesions throughout the spleen (Figure 2) and liver.

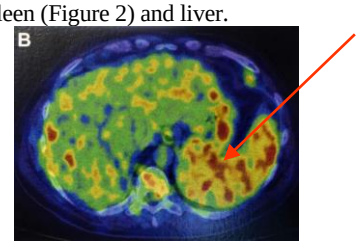


Figure 2. Axial CT shows increased metabolic activity in multiple nonenhancing hypodense splenic lesions.[12]

An extensive workup did not reveal malignancy, but did find an IgA deficiency. A biopsy of a liver lesion was compatible with *Bh* infection on silver stain. Subsequent *Bh* IgG serology was positive at a titer of >1:1,024. He was treated at home with IV Gentamicin for 2 weeks followed by oral doxycycline BID for 4 weeks for a total of 6 weeks. All lesions significantly improved on CT scan 8 weeks later. The authors concluded that *Bartonella* was likely the cause of the original pulmonary nodules 4 years earlier and was misdiagnosed.

Study 8: This study consisted of 29 cases of *Bartonella* infection in solid organ transplant recipients. Diagnosis was made by culture 2/4, PCR 12/14, silver stain 12/19 and serology 23/23. Time to infection was 5.6 ±5.3 years for CSD, but 2.7±2.4 years for atypical CSD. All 8 patients with CSD and 19 of 21 patients with atypical CSD were cured with antibiotic therapy. The other 2 patients with endocarditis died. The authors concluded that *Bartonella*-infected transplant recipients respond well to antibiotic therapy even though they are immunosuppressed.

Bartonella Disease Therapy:

Bartonella-disease therapy has 2 components: 1) elimination of *Bartonella* infection and the 2) clinical response of the *Bartonella* disease. The human cases of atypical CSD in humans reviewed here had the same therapy recommendations and etiological and clinical evaluations of *Bartonella* therapy that we have recommended for the past 20 years for cats. Many others still do not recommend testing and treating infected healthy cats, but do recommend testing and treating cats with inflammatory diseases. Therapy of feline *Bartonella* infection and diseases is relatively easy. We recommend oral azithromycin at 10mg/kg once daily for 21 days or longer. However, there are other excellent choices of antibiotics as well. We have reported successful therapy results in approximately 88% of cats with *Bartonella* infections.[14]

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More than 5,000 *Bartonella* references can be obtained at: **www.nlm.nih.gov/**