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NEWSLETTER

Bartonella is not a "Lily-Livered" Pathogen©

Evelyn E. Zuckerman, Editor **Spring 2016** **Vol. 15, Number 2**

In This Issue:

The Spring 2016 issue of the NVL Newsletter will review the association of feline derived *Bartonella henselae* with liver diseases. Liver *Bartonella* diseases, consisting of granulomas and peliosis, are not common but can be life-threatening, in humans, dogs, and cats.

Basic Concepts:

The liver is the largest organ and gland in the body of all animals. It processes most of the nutrients absorbed by the intestines and converts those nutrients into forms that can be used by the body. It then oversees the composition of the amounts of glucose, protein, and fat that enter the bloodstream. It makes cholesterol and important proteins, such as albumin and clotting factors. The liver also stores glucose and vitamin A, iron, and other minerals. It removes bilirubin, the by-product of the breakdown of hemoglobin from worn out erythrocytes, is a volume reservoir for blood, cleans bacteria from blood, all which makes the liver susceptible to *Bartonella* pathogensis since they are intra-erythrocyte parasites.

The liver is a highly vascular organ which receives a dual vascular supply; the hepatic portal vein brings to the liver all of the blood which has previously passed through the intestine and spleen while the hepatic artery brings fresh, oxygenated blood from the aorta. Portal venous blood from the intestine and spleen and arterial blood from the aorta mix together in hepatic sinusoids before leaving the liver via the hepatic vein. The liver receives over 25% of the total resting cardiac output and is responsible for over 20% of the body's resting oxygen consumption. The high vascular nature of the liver makes it prone to the pathologic effects of *Bartonella* as they have an infinity to infect erythrocytes and vascular endothelial cells of capillaries.

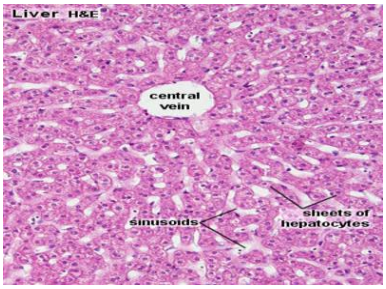
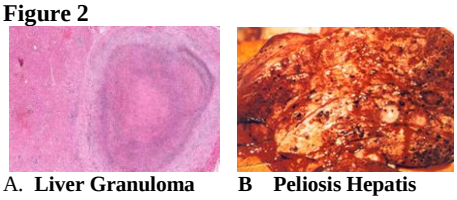


Figure 1 Normal liver histology
Hill, M.A. (2016) Embryology *Liver histology 001.jpg*. https://embryology.med.unsw.edu.au/embryology/index.php/File:Liver_histology_001.jpg

The liver is organized into lobules that take the shape of polygonal prisms. Each lobule is typically hexagonal in cross section and is centered on a branch of the hepatic vein (the central vein). Within each lobule, hepatocytes are arranged into hepatic cords separated by adjacent sinusoids. The fenestrated endothelium lining the sinusoids lies immediately adjacent to the cords, with no basement membrane and practically no intervening connective tissue, so that each hepatocyte is bathed on two faces by blood plasma.
http://www.siumed.edu/~ dking2/erg/liver.htm

The characteristic feature of *Bartonella* liver pathology is inflammation leading to granulomas, microabscesses, and peliotic lesions. Granulomas consist of areas of necrosis with accumulations of macrophages and lymphocytes (Figure 1A). Peliosis hepatis is a vasculoproliferative process with blood engorged cystic areas in the liver tissue and vascular tumor formation (Figure 1B).[1]

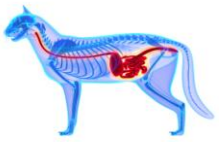
Figure 2



A. **Liver Granuloma** **B Peliosis Hepatis**

Cats:

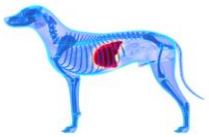
Bartonella henselae causes liver disease in cats, the natural reservoir host. However, the disease spectrum differs in cats compared to dogs and humans.



In cats there has not been an association of *B. henselae* with peliosis hepatis cases. A study of 26 cats with peliosis hepatis did not detect *B. henselae* in any lesions using an antigen detection method and PCR.[2] However, *B. henselae* did cause hepatic granulomas and hepatitis in 9 of 13 (69%) experimentally infected SPF cats.[3] In addition, we found 148 of 330 (45%) cats with hepatitis with elevated liver enzymes, to be *B. henselae* positive by our Fe*Bart*® Test.[4] 60% of these cats responded well to azithromycin therapy.[5]

Dogs:

There have been several reports of *Bartonella* induced liver diseases in dogs. We assisted in a recent publication of a dog with peliosis hepatis from the Oradell Animal Hospital in Paramus, NJ, where we began our veterinary *Bartonella* clinical studies.[6]



Peliosis Hepatis (PH):

A 3-year-11-month-old mixed breed dog presented with progressive lethargy and vomiting.[6] Abdominal ultrasonographic examination showed moderate ascites. Exploratory laparotomy revealed a large volume of non-clotted blood and blood-filled vesicular lesions throughout the liver. Biopsy revealed peliosis hepatis and the WB (Fe*Bart*® Test) was a strong +4 positive. Treatment with azithromycin for 6 weeks resulted in complete recovery with no recurrence. There was an 8 fold titer reduction in the post therapy comparative titration test, performed 6 months after the end of therapy, indicating elimination of *Bartonella* infection. There has been no recurrence more than a year later.

The first published case of PH occurred in a 6-year-old Golden Retriever with general weakness and 5L of abdominal fluid, and multiple small liver nodules and cysts. The dog died under anesthesia and was PCR positive for *Bartonella henselae* DNA in the liver.[7]

Granulomas:

Several reports of liver granulomas have been published. The first occurred in 2 dogs, PCR positive for *B. henselae* and *B. clarridgeiae*, with abnormal liver values who recovered fully after azithromycin and other medications.[8] Another case occurred in an 8-year-old Rottweiler who had systemic granulomatous disease involving the liver, spleen, heart, lymph nodes, omentum, kidney, lung, mediastinum, and salivary glands. *B. henselae* and *B. vinsonii* subsp. *berkhoffii* DNA were found in the tissues. The dog did not respond to unspecified antibiotic therapy and was euthanized.[9]

We found 23 of 221 (10.4%) dogs with liver disease were Fe*Bart*® WB *Bartonella* positive. This is one-quarter the incidence of cats with *Bartonella*-induced liver disease.

Humans:

Bartonellosis, the spectrum of *Bartonella* spp. diseases, in humans can occur as classical cat scratch disease (CSD) or CSD with sequelae or sequelae only. A common *Bartonella* sequelae is involvement of the liver and spleen, often concurrently, due to the hematogenous spread of the bacteria via erythrocytes. This occurs more frequently in humans than in dogs or cats and can be especially severe in immunocompromised people- chemotherapy patients, HIV infected people or the aged.[10-15] The full spectrum of granulomas, microabscesses and peliosis hepatis occur in both immunocompromised and immunocompetent adults and children. Hepatic inflammation can manifest clinically as periumbilical or upper abdominal pain, weight loss, and hepatomegaly, often in conjunction with splenomegaly. Typical imaging findings are hypoechoic random size lesions by ultrasound and hypoattenuating lesions on CT.[14]

Granulomas:

There are multiple reports of hepatic granulomas in adults and children caused by *B. henselae*. In one retrospective study of 7 patients, all diagnosed serologically, treatment with macrolides or combinations of 2 antibiotics for at least 2-3 weeks, led to rapid clinical improvement and cleared the infection, although the hepatic lesions persisted for several months or years.[16] Another case occurred in an immunocompetent 12 year old boy with fever, abdominal pain and weight loss who had played with a kitten. He recalled no scratch or bite from the kitten, had no skin papule but did have bilateral inguinal lymphadenopathy. This was a case of systemic bartonellosis, CSD with concurrent sequelae. Diagnostic findings included elevated liver enzymes, abdominal MRI showed multiple liver lesions and he was seropositive for IgM and IgG anti-*B. henselae* antibody at 1:100 and 1:320 respectively. Ultrasound guided liver biopsy was performed and histopathology revealed granulomas with areas of necrosis and the Warthin-Starry silver stain was positive for rod-like bacteria. He recovered with IV gentamicin and oral rifampin.[17]

An adult case of granulomatous hepatitis occurred in a 36-year-old immunocompetent women. This case demonstrated the difficulty in diagnosing *B. henselae* as the etiological agent.[18] She initially presented in August of 2008 with abdominal pain and mildly elevated liver enzymes. She was negative for antibodies to *B. henselae* and *B. quintana* by IFA. Untreated, she had relapses in July of 2009 and finally in May of 2010. Blood cultures were sterile during these periods and she finally was diagnosed by PCR and blood culture on her final recurrence. Multiple antibiotic therapy including azithromycin, ciprofloxacin, and clarithromycin failed to eliminate her infection. A partial liver lobectomy was positive by PCR and immunochemistry for *B. henselae* as the etiologic agent. The patient then reported having had contact with a cat before the illness began but did not recall any scratches or bites. This case exemplifies the difficulty in diagnosing some cases of bartonellosis, especially when seronegative and when no report of cat contact was obtained.

Peliosis Hepatis (PH):

Mosepele and colleagues have an excellent review on human *Bartonella* vascular infection and vasoproliferative effects.[19] *B. henselae* can cause bacillary angiomatosis (BA) which is cutaneous vascular nodules, that when found in the liver, are called peliosis hepatis (PH). PH is a condition consisting of multiple small blood-filled cysts of the liver sinusoids. Patients show chronic epigastric pain. They can be diagnosed by CT scans that show multiple hypodense areas in the liver. The cysts are engorged blood filled areas that appear tumor-like, and in extreme cases can rupture. PH occurs more often in immunocompromised patients such as transplant patients, patients receiving long-term chemotherapy and HIV-1 infected people.

Most pathogenic bacteria cause tissue destruction, in order to achieve wider distribution in the body, by inducing apoptosis (cell death) in the infected host cells. *B. henselae* persist in the periendothelial extracellular matrix resulting in extended replication. This persistence allows the bacteria to secrete effector proteins (BepA and BepA2) which bind to the endothelial cell membrane receptors. This induces an anti-apoptotic state (anti-cell death) allowing the endothelial cells to proliferate rather than die. This is a very unique pathogenic mechanism.

In the late 1980's, while we were at the Albert Einstein College of Medicine, we studied a severely ill HIV-infected homeless patient with BA and PH who was admitted to the affiliated Bronx Lebanon Hospital.[20] Due to our past research with feline retroviruses, FeLV and FIV, we were studying HIV-1 and HTLV-1 retroviruses in people. Thus, as a veterinarian working in a medical center, we knew this was an important feline zoonotic agent to investigate. Working collaboratively with physicians in the Infectious Disease Service, we developed methods to test cats for *Bartonella*. This patient with bartonellosis, in the early era of the AIDS epidemic, had been disowned by his family and friends and found the only companion who would accept him, a stray kitten from the streets of the South Bronx. Unfortunately, that loving kitten was infected with *Bartonella* and infected his protector causing life-threatening illness of BA and PH. Fortunately, the physician attending this patient was one of the earliest physicians describing and treating patients with AIDS in NYC and recognized the bartonellosis syndrome. The patient was treated with erythromycin and recovered from his bartonellosis and we treated the kitten with doxycycline which eliminated the infection.

Conclusion: Feline *Bartonella* spp. can cause life-threatening liver disease in cats, dogs and people and veterinarians can, and should, make their cat owner clients aware of this zoonosis.

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***Bartonella* references can be obtained at:**
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