PEER REVIEWED

Lyme Nephritis Review

Lisa M. Sepesy, MPH, VMD, DACVIM (Internal Medicine)
Pittsburgh Veterinary Specialty & Emergency Center
North Hills, Pittsburgh, PA

Exposure to *Borrelia burgdorferi* (Bb) is common, but less than 5% of exposed dogs show classic clinical signs.[1] As a result of climate change, increasing travel, increased proximity to deer and wildlife, and bird migration, tick exposure to both humans and pets has increased. The *Ixodes* tick is responsible for transmission of Bb along with other tick-borne diseases.[1,2] Despite precautions, preventatives, and vaccines, some dogs develop clinical illness from Bb. The most common manifestation of illness is polyarthropathy. In most instances, Bb exposure is found incidentally on annual serologic screening tests. In other instances, serologic screening may be specifically ordered due to clinical signs of illness. This article will briefly review the more complicated case of Lyme nephritis and treatment in dogs.

Borrelia burgdorferi is a tick-borne spirochete organism first identified in 1975 in Lyme, CT. In humans, the clinical signs can be severe, including flu-like symptoms, fever, skin rashes, and chronic illness, such as arthritis, and cardiac and neurologic symptoms. In contrast, the majority of dogs with exposure to *Borrelia burgdorferi* (Bb) have no clinical signs. If present, clinical signs can include lameness, fever, and anorexia. Often, these signs will be self-limiting or, if treated rapidly, responsive to antibiotic therapy.[2, 3, 4] Cases of neurologic, ocular, and cardiac complications of lyme disease are not well documented in dogs.[3, 5, 6]

Lyme nephritis

Lyme nephritis (LN) is rare and only occurs in approximately <1-2% of Lyme positive cases, with Labradors and Golden Retrievers being overrepresented.[1, 2, 4] Experimental models of Lyme disease failed to show renal disease or proteinuria, making study of this disease difficult.[1, 2] No experimental model for Lyme nephritis exists.[1, 2, 4]

The presentation of LN can vary widely with the duration of clinical signs ranging from 2 weeks to 6-8 weeks, on average.[1, 4] Signs can include vomiting, lethargy, and anorexia or, more severely, fever, weight loss, ascites, effusions, or edema.[1] Protein-losing nephropathy (PLN) of any type includes proteinuria, hypoalbuminemia, and when afvanced often azotemia, along with hypertension and hypercoagulability.[1,2,4] In the severe cases, signs can often progress quickly, and death can occur due to secondary complications within weeks. Serologic evidence of Bb exposure and proteinuria alone is not pathognomonic for Lyme nephritis and other causes of proteinuria must be excluded. Elevations of the urine protein creatinine ratio (UPC) can be secondary to urinary tract infections, amyloidosis, immune mediated disease, neoplasia, genetic disease, or toxins.[1] Renal biopsy, if done early in the disease, can aid in diagnosis and allow early intervention and treatment.

Unlike leptospirosis, the renal changes associated with Lyme nephritis are not due to the organism itself but rather an immune mediated process. Renal biopsies from moderate to severely affected dogs revealed immune mediated membranoprofliferative glomerulonephritis (MPGN), tubular necrosis/regeneration, and interstitial inflammation, along with subendothelial C3, IgG and IgM deposits.[1, 7, 11] These findings are different from those seen in other types of glomerulonephritis.[11] Immunohistochemical (IHC) staining of renal biopsies show some positive staining with antibodies directed against Bb antigen, but overall results were discordant with PCR for Bb and seemed to point toward immune complex disease rather than direct spirochete involvement.[14] Studies have shown LN to be a result of the immune complex disease and not directly related to the presence of the pathogen.[14, 13]

A study was done in 2008 to evaluate for the presence of the B burgdorferi organisms in the kidneys of serologically Lyme positive dogs.[9] Twenty-six affected dogs and 10

control dogs were evaluated, and there was minimal evidence of the presence of Bb or other bacterial organism in the renal tissue of the dogs suspected of Lyme nephritis.[8] Studies to detect *Borrelia burgdorferi* DNA in tissues in Lyme positive or Lyme suspect dogs was low at only 7% of the 38 dogs affected. The study concluded the DNA was rarely found in tissues from naturally infected dogs and there was no correlation between the IHC staining and results of the PCR assay in renal tissues.[13] The positive IHC staining can be consistent with antigen leading to immune complex disease, even when the pathogen is cleared.[14] Only rare renal tissues were positive for spirochete DNA, even when the dogs had strong clinical and pathologic evidence of LN. These finding lend support to the immune mediated process of glomerulonephritis in these dogs.[7, 13, 14]

The diagnosis of Lyme disease as mentioned, is not straightforward and is based on positive serology, a history of exposure to *Ixodes* spp., presence of the disease in the region, and compatible clinical signs and most importantly, exclusion of other causes.[1] There several patient side/POC tests for Bb such as the Idexx 4Dx Snap Test which also test for other tick borne diseases. A C6 (Idexx) antibody test is a quantitative test for Lyme disease which can detect antibodies at 3-5 weeks after infection and can remain positive for over 6 months. The level of antibody detected, however, does not correlate to severity of disease. The updated Lyme Consensus statement reports that 4/6 panelist suggest to check for a decrease in C6 levels after treatment, but there is no agreement that it should be used to guide treatment or evaluate responses.[2] Per the laboratory's instructions, if treated dogs are retested 6 months after infection, the C6 level should be <50% of pretreatment levels.[1, 2, 4] Cornell University's Multiplex Assay measures different outer surface proteins, A, C, and F. These outer surface proteins

help differentiate vaccination, as well as early or chronic infection. Antibodies to OspA serve as markers for vaccination, as OspA is generally only expressed by Bb within the tick and not expressed on Bb transferred to the dog. OspA is a component of all Bb vaccines, while OspC and OspF serve as markers of infections. OspC is present approximately 2-3 weeks after infection and levels start to decline after 2-3 months. They are then undetectable by 4-5 months post-infection. The OspF outer surface protein is an indicator of chronic infection and is detectable by weeks 5-8 post-infection. OspF and C6 antibody have a close correlation.[7]

Treatment

There is no consensus on the best treatment for Lyme nephritis.[1,2,3] If a dog presents asymptomatic and Bb serology positive, a urinalysis should always be performed to evaluate for proteinuria. If the urine is culture negative yet proteinuric, then antibiotic therapy and appropriate therapy as needed for proteinuria or PLN should be initiated.[1, 2, 3, 4] Doxycycline is the most frequent choice at 10mg/kg PO q24h for 30 days. Other potential therapies include amoxicillin 20mg/kg PO q8h for 30 days and cefovecin (Convenia) 8mg/kg SC q14d for two doses.[5] Doxycycline is the preferred antibiotic because it covers other diseases also spread by *Ixodes* spp ticks such as anaplasmosis. Obviously other causes for PLN should be tested specific to the geographic area and the clinical signs. Leptospirosis can often mimic signs of PLN and serology testing should be submitted. Early cases of Leptospirosis can have nega-tive titers and convalescent titers should be checked in 2-4 weeks. A full vector-borne disease panel is recommended to screen for other infectious agents (*Ehrlichia, Babesia, Bartonella, Anaplasma,* and others pending geographic location) as Bb seropositivity indicates prior tick exposure.

A cortical renal biopsy, although needed for confirmation of active immune complex disease, is not always an option.[1, 2, 3] The risks associated with the procedure must be considered, which include bleeding, worsening azotemia, and thrombus. If the disease progresses, or there is worsening azotemia and hypoalbuminemia, then therapy for PLN along with immunosuppression therapy is recommended.[2, 3] If the patient is still eating and drinking, oral medications can be prescribed, including appropriate antibiotics, antithrombotics, antihypertensives, ACE inhibitors, or angiotensin receptor blockers, along with renal diets and phosphate binders. Subcutaneous fluids can be used judiciously in some cases with monitoring for fluid overload and edema. If azotemia with anorexia, nausea, and vomiting, and worsening clinical signs continues, supportive care and hospitalization is needed. Due to the associated hypoalbuminemia, however, crystalloid fluid therapy may not be an option and will only result in further third spacing, edema, and fluid overload. Oncotic support can be provided with colloids or albumin transfusion and further supportive care provided with IV administration of antibiotics, antinausea medications, antacids, and gastroprotectants. Additionally, feeding tubes can be used to provide nutrition and enteral fluids for hydration.

Immunosuppressant therapy based on the GN study group guidelines includes mycophenolate (7.5-10 mg/kg PO every 12 hours) and a tapering course of prednisone (1 mg/kg bid for 4 days, with a 2 week taper) .[1, 2, 3] Other immunosuppressants can be used if mycophenolate is not tolerated but there is no consensus on which drug is preferred.[2] Gastrointestinal side effects are the most common adverse side effect of mycophenolate which can often be avoided with dose reduction.

Success in treatment can vary, with some dogs succumbing to disease early in its presentation. Other dogs will stabilize but with ongoing proteinuria and/or azotemia. Although a rare presentation of Lyme disease, a diagnosis of Lyme nephritis can be devastating news with a poor prognosis,[1] but there is some hope in present treatments and aggressive supportive care. It is important to try to diagnose early, as well as rule out other treatable diseases with a better prognosis. Prevention of Lyme disease with year-round tick control and vaccination is essential to minimize the risk of Lyme polyarthritis or Lyme nephritis.[9,15]

1. Littman, MP. Lyme nephritis: State of the Art Review. J Vet Emerg Crit Car. March 2013 1-11.
2. ACVIM consensus update of Lyme borrelliosis in dogs and cats. J Vet Intern Med 2018 32; 887-903.
3. Consensus Recommendations for immunosuppressive Treatment of Dogs with Glomerular Disease based on established Pathology, IRIS Canine GN Study Group Establish Pathology Sub-group. J Vet Intern Med 2013 27;544-554.
4. Littman MP, Goldstein RE, Labato MA, et al. ACVIM Small Animal Consensus Statement on Lyme Disease in Dogs: Diagnosis, Treatment and Prevention J Vet Intern Med 2006 20; 422-434
5. Levy S, Duray Complete heart block in a dog seropositive to *Borrelia burgdorferi* J Vet Int Med 1988; 2: 138-141
6. Raya al. Afonso JC, Perez-Ecija RA Orbital Myositis associated with Lyme disease in a dog Vet Rec 2010 167: 663-664
7. Grauer GF, Burgess EC, Cooley, AJ, et al. Renal lesions associated with *Borrelia burgdorferi* infection in the dog. J Am Vet Med Assoc 1988; 193; 237-239
8. Cornell University College of Veterinary Medicine Animal Health Diagnostic Center, Lyme Disease Multiplex Testing in Dogs
9. Hutton TA, Goldstein RE, et al. Search for *Borrelia burgdorferi* in kidneys of dogs with suspected Lyme nephritis. J Vet Int Med 2008; 22; 860-865
10. Lafleur RL, Callister SM, et al. Vaccination with the osp A and osp B negative *Borrelia burgdorferi* strain 50772 provides significant protection against canine Lyme disease. Clinical and Vaccine Immunology. July 2015 22; 7. 836-839
11. Dambach DM , Smith CA, Lewis RM et al. Morphologic immunohistochemical and ultrastructural characterization of a distinctive renal lesion in dogs putatively associated with *Borrelia burgdorferi* infection 49 cases (1987-1992). Vet Path 1997; 34; 85-96.
12. Wagner B, Johnson J, et al Comparison of effectiveness of cefovecin, doxycycline and amoxicillin for the treatment of experimentally induced early Lyme borreliosis in dogs. BMC Veterinary Research 2015 11; 163 1-8
13. Travail V, Cianciolo RE, et al. Mycophenolate mofetil and telmisartan for the treatment of proteinuria secondary to minimal change disease podocytopathy in a dog. J Vet Intern Med 2022; 1-2
14. Chou J, Wunschmann A Hodzic E et al Detection of *Borrelia burgdorferi* DNA in tissues from dogs with presumptive Lyme Borreliosis. J Am Vet Med Assoc 2006 229; 1260-12699.
15. Baker CF, McCall JW, et al. Ability of an oral formulation of afoxolaner to protect dogs from *Borrelia burgdorferi* infection transmitted by wild Ixodes scapularis ticks. Comparative immunology, Microbiology and Infectious Diseases. 2016 49;65-69