Bella's Not So Pretty Problem

A Case of Lyme Nephritis in a Canine Patient

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Introduction

Lyme disease is caused by *Borrelia burgdorferi* (Bb), a unicellular microaerophilic gram-negative motile spirochete (8,9). The main tick vector for Bb is the 3- host tick, *Ixodes scapularis* in Mid-Atlantic, Northeastern, upper Midwestern states, and adjacent areas of Canada (9). The geographical persistence and spread of Bb is related to the 2-year, 3-stage life cycle of its vector, where one blood meal occurs per stage and a variety of hosts may be fed upon (7). Ixodes larvae acquire Bb during their first meal, usually in the summer, from a Borrelia-infected small mammal, specifically mice or squirrels but also, birds (11). The prevalence of Bb in nymphal or adult ticks may reach upwards of approximately 50% in endemic geographical areas (5). Borrelia infection usually occurs in the warmer months due to the questing behavior of Ixodes and the recreational habits of humans and their dogs (11). It takes usually 36-48 hours of attachment to allow Bb to migrate from the midgut of the tick and into the host (7). Most dogs that are seropositive for Bb show no clinical signs. However, when animals are clinical, the two main manifestations are Lyme arthritis and Lyme nephritis (LN). Treatment of a protein losing nephropathy (PLN) due to Lyme disease is tricky in that there is no way to definitively diagnose LN until post mortem examination, making it a diagnosis of clinical suspicion and exclusion (9). Clinical issues associated with this manifestation of Lyme disease can be numerous and severe, making treatment complicated and prognosis guarded in those that are clinically unstable.

History and Presentation

Bella was an almost 4 year old female spayed Beagle mix that was presented to the Red Bank Veterinary Hospital's emergency service on the evening of Tuesday, January 1, 2019, for a two week history of vomiting, hyporexia, and losing weight. Although her owners were only offering her dry kibble, she was uninterested in it, but would occasionally eat table scraps. After eating, usually a couple hours post, she would vomit mucus and food. Her energy level over the past week or so prior to presentation had a waxing and waning quality, but not noticeable enough for the owners to be concerned. On the day of presentation, she began shaking and was acting more lethargic than normal, as she was looking dull and not wanting to open her eyes. Owners noted that she was not drinking as much water as she normally did but seemed to be urinating more. She had no history of chewing her toys or getting into anything of which owners were aware. No diarrhea, coughing, or sneezing were reported. She would go on walks in the woods, drink from puddles, and the owners had seen ticks on her. She only received flea/tick prevention during the summer months and was not up to date on her vaccinations. She had no other major medical problems prior to this and had not been to a veterinarian since she was adopted at 8 weeks old from a rescue that brought her to New Jersey from the southern states.

On presentation, Bella was quiet, alert, and responsive with vitals within normal limits. Her temperature was 100 degrees Fahrenheit, she had a heart rate of 110 beats per minute with no murmur or arrhythmia, and a respiratory rate of 22 breaths per minute with clear bronchovesicular sounds in all fields. She was approximately 5% dehydrated and had a body condition score of 4/9. Her mucous membranes were pink with a capillary refill time of right at 2 -seconds. No oral masses or foreign bodies were seen, but she did have moderate dental tartar. She was given a pain score of 2/4 due to her abdomen being tense and painful on caudal abdominal palpation as she turned to try and bite. No masses were felt, however, and her rectal

exam was within normal limits. She had a decent hair coat with no petechiation or ecchymosis noted on her skin. No cranial nerve deficits were seen. She was fully ambulatory in all four limbs and no spinal or joint pain could be elicited.

Blood was taken to perform an initial CBC and chemistry panel as well as to put some on hold to send out a CBC with pathology review, a NCSU tick panel, and tick titers. Her CBC was largely unremarkable other than a severely decreased platelet count of 14 K/uL (148-484). A manual count was performed following this result that showed 0-1 platelet per HPF for a total of 15,000 platelets, confirming the low number on CBC. Her chemistry panel showed a severely elevated BUN of 79 mg/dL (7-27), a severely elevated creatinine of 7 mg/dL (0.5-1.8), a moderately elevated phosphorus of 12.3 mg/dL (2.5-6.8), and a moderately elevated amylase of 1728 U/L (500-1500). Abdominal radiographs were taken and were unremarkable with no evidence of a mass, foreign body, or obstruction. Abdominal and thoracic FAST scans were performed and showed no pericardial, pleural, or abdominal effusion. Blood pressure was obtained via Doppler and showed a mean arterial pressure of 190 mmHg. Free catch urine was put on hold for a urinalysis to be done in the morning and some was also taken, via cystocentesis, for culture. It was suspected, however, based on the blood work and lack of significant dehydration or any obstructions, that we were dealing with an acute kidney injury (AKI) resulting in renal azotemia.

Findings were discussed with the owner and due to severity of azotemia and thrombocytopenia along with her history of vomiting and hyporexia, they elected to hospitalize her for management and further work up with the Internal Medicine service. She was started on 5 ml/kg/hr LRS, Cerenia at 1 mg/kg q12h, pantoprazole at 1 mg/kg q12h, enrofloxacin at 10 mg/kg q24h, doxycycline at 5 mg/kg q12h, and hydromorphone at 0.05 mg/kg q6h as needed. She was

offered food at 8pm that night but did not eat and food was pulled at midnight before having an abdominal ultrasound the next morning. As her blood pressure was 190 mmHg on intake, she was signed up for a recheck blood pressure at 3am that showed a BP of 260 mmHg. She was given a 0.1 mg/kg dose of amlodipine and BP was checked 1 hour post but was only down to 250 mmHg. Her blood pressure never dropped below 230 mmHg during the night even with a second dose of amlodipine given. No neurologic or ocular signs were evident, so her BP continued to be monitored.

Upon transfer to Internal Medicine in the morning, a 4Dx SNAP was run as well as a urinalysis (with free catch urine). The 4Dx results came back as positive for Lyme with the urinalysis showing 3+ protein, 3+ blood, and a urine specific gravity of 1.029. Lyme nephritis (LN) was suspected based on these results, and her work up continued throughout the day.

Pathophysiology

Unlike leptospirosis, LN is not due to renal invasion of spirochetes but due to immune mediated glomerulonephritis with Lyme-specific antigen-antibody complex deposition in the glomerulus (1,8-10). Subendothelial glomerular immune complex deposition may occur due to passive entrapment of antigens or circulating complexes in previously altered or normal glomeruli (1,8). Complexes then attract inflammatory cells or activate resident glomerular cells to release vasoactive substances, proinflammatory cytokines, and activators of platelets and the complement cascade which in turn attacks cell membranes (8). Secondary tubular changes may be due to hypertension and efferent arteriole vasoconstriction, tubular hypoxia, or toxic proteins in the glomerular filtrate (2,8). Very few, if any, organisms can be found by staining or by using

PCR in kidneys of dogs with LN (3,9). However, Lyme antigens, DNA, and sometimes organisms have been found in tubular cells and in urine (3,4,10). Renal biopsies from Lyme positive dogs with severe proteinuria, hypoalbuminemia, and kidney failure show membranoproliferative glomerulonephritis with subendothelial C3, IgM, and IgG deposits, diffuse tubular necrosis/regeneration, and lymphocytic-plasmacytic interstitial nephritis (1,2). There are no validated staining techniques available to prove that glomerular immune complexes found in kidney biopsy specimens are Lyme-specific in the living dog, making diagnosis depend on Bb-seropositivity and other supportive clinical findings in a dog with PLN in which no other cause can be identified.

Diagnostic Approach/Considerations

Lyme nephritis and associated PLN is an uncommon, but is the most serious, presentation of Lyme borreliosis with it being seen in <1-2% of dogs that are seropositive for Lyme (8). In comparison, about 30% of Lyme positive dogs have a history of lameness (9). As such a low number of Lyme positive animals have signs of or experience severe consequences of proteinuria, other non-infectious causes for PLN such as neoplasia, amyloidosis, as well as genetic, toxic, or other causes must be considered (9). Thus, a thorough diagnostic evaluation is still warranted to rule out other or concurrent diseases, and to stage and characterize possible complications of PLN. Unfortunately, this disease is incompletely understood as there is no experimentally inducible model to study predisposing factors, pathogenesis, onset, progression, treatment, or prevention (3,4,9). Diagnosing Lyme exposure can easily be done bedside with the IDEXX SNAP 4DxPlus and/or as a send out Lyme quantitative C6 antibody test (9). The Lyme quantitative C6 antibody test works similarly to the Lyme portion of the bedside 4Dx Plus, but

provides an antibody level (similar to a titer). The C6 peptide represents one of the constant, or invariable regions of an outer an outer surface protein on Bb. This protein is only encoded by genes that are active in a mammalian host, therefore this test does not cross-react with vaccination making any antibodies to the C6 peptide indicate natural infection. The quantitative assay, since it gives an actual number, can be monitored in those patients that are responding to treatment as it should fall as the patient clears the infection. These two methods are the most common and both were used in this case.

Dogs with Lyme positive protein losing nephropathy may present with dramatic emergent signs, just as dogs with any type of protein losing nephropathy, including thromboembolic events, hypertension, effusions/edema, or signs of kidney failure (ie – hyporexia/anorexia, vomiting, pigmenturia, oliguria/anuria) (8,9). Nephrotic syndrome, another possible sequela of severe glomerulonephritis, is defined as the presence of proteinuria, hypoalbuminemia, hypercholesterolemia and either edema or ascites. Patients may have any or all of these signs, but it is impossible to predict how each patient will present. For clinically stable dogs with only mild changes due to PLN (ie – mild hypoalbuminemia and/or nonprogressive, uncomplicated renal proteinuria, without azotemia) recommendations include antimicrobial treatment with doxycycline and management of proteinuria, hypercoagulopathy, and hypertension (6). These may include an angiotensin-converting enzyme (ACE) inhibitor or aldosterone receptor blocker, antithrombotics, antihypertensives, protein and phosphorus-restricted diets, and omega-3 fatty acid supplementation, as needed (6,9). For dogs with more persistent, progressive, or severe glomerular disease, or complications such as vomiting, dehydration, edema/effusions, or worsening azotemia, additional recommendations include antiemetics, crystalloids or colloids based on need and how the patient handles fluids,

aldosterone antagonist diuretics, phosphate binders, and treatments for AKI as needed (6). In addition, immunosuppressive therapies are indicated in those not responding to treatment or those with rapid progression, severe hypoalbuminemia (serum albumin concentration<2.0 g/dL) or severe azotemia (serum creatinine concentration >5 mg/dL) (6,9). Single drug or combination treatment consisting of rapidly-acting immunosuppressive agents are recommended in addition to antimicrobials (doxycycline for LN) and standard PLN treatments and diets (6). For both slowly or rapidly progressive forms of PLN, therapeutic efficacy is assessed by serially monitoring blood pressure, proteinuria, serum albumin concentration, and kidney function parameters. In the absence of significant adverse effects, at least 12 weeks of immunosuppressive drug treatment should be initiated before altering or abandoning the immunosuppressive trial (6,9). The IRIS Study Group recommended mycophenolate as the first immunosuppressive employed, sometimes with an added tapering dose of prednisolone in dogs with acute, rapidly progressive, glomerular disease (6).

Case Summary and Outcome

Following the results of the 4Dx SNAP and urinalysis on January 2nd, a urine protein:creatinine ratio was submitted that morning and returned as severely elevated at 10.3 (<0.5-0.5). Repeat CBC and chemistry panel were submitted to assess any change that may have occurred over night after the addition of medications and fluids, particularly her severe azotemia and thrombocytopenia. CBC showed minimal improvement of her platelet numbers at 17 K/uL (170-400). Similarly, the chemistry showed little improvement with a BUN of 73 mg/dL (7-27), creatinine of 6.3 mg/dL (0.5-1.8), and a phosphorus of 12.2 mg/dL (2.5-6.8). A full abdominal ultrasound was performed and revealed no abnormalities, which was expected at this point. An

IDEXX Lyme quantitative C6 antibody test was submitted to confirm our suspicion of Lyme disease causing nephritis. We also received the results of our leptospirosis titers and Bella was negative for all tested serovars. A second antibiotic was added as Unasyn (ampicillin/sulbactam) at 22 mg/kg. She was also started on 0.3 mg/kg amlodipine orally as her blood pressure was fluctuating throughout the day between 165-200 mmHg.

On January 3rd, her Lyme quantitative C6 antibody test results returned with a value of 216 U/mL. IDEXX recommends levels above 30 U/mL to be clinically significant enough to warrant treatment. Her urine culture also returned with no growth. These results, along with the results of the entire work-up, was strongly supportive of the likelihood that her PLN was due to her Lyme disease, as she had no other obvious comorbidities that could be causing the illness. A recheck CBC was not performed again as money was beginning to become an issue. A recheck chemistry was performed, however, to assess her azotemia as well as her phosphorus. All three values were decreased on this panel with BUN to 63 mg/dL, creatinine to 6.1 mg/dL, and phosphorus to 9.4 mg/dL. She began to regurgitate throughout the day having four total episodes and had to have food withheld. She was still having normal urine and bowel movements during the day. Her last episode of regurgitation was around 7pm so at 3am she was offered a small amount of chicken and rice which she kept down. She was also offered water began drinking rapidly and regurged some of that. She began reverse sneezing after the water regurgitation. Ondansetron at 0.5 mg/kg was added as a second antinausea medication.

By early morning on the 4th she was noted to have mild peripheral limb edema in all four limbs. Her fluids were dropped to 30 ml/hr, which was half of her previous fluid rate. Her hypertension had become refractory to the amlodipine at 0.3 mg/kg with her BP staying consistently at 205 mmHg so her dose was increased to 0.4 mg/kg. She also began to have

diarrhea and was started on metoclopramide at 2 mg/kg/day and two scoops of clay to be given twice daily. She had no more interest in food and her regurgitation had begun to progress to vomiting even with the two antinausea medications. Upon arrival of her managing clinician, a repeat abdominal ultrasound was ordered as well as a recheck chemistry panel. Her fluids were also further dropped to 20 ml/hr as her peripheral limb edema was progressing. Her abdominal ultrasound was again unremarkable. Her blood work, however, was not. Her BUN was increased to 74 mg/dL, creatinine to 6.4 mg/dL, and her phosphorus was higher than it had ever been at 14.1 mg/dL.

Throughout the morning, Bella continued to decline. She was becoming more lethargic, anorexic and her peripheral limb edema was becoming worse even on her low rate of LRS. Due to the poor response to treatment and the renal failure, her owners elected to humanely euthanize. Before passing, however, she was taken to her favorite park to play in the sun with her family and eat all of the McDonald’s cheeseburgers she could handle.

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