Lyla's Down in the Dumps

A Case Report

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Introduction:

Inflammatory Bowel Disease (IBD) is characterized as an abnormal accumulation of various types of white blood cells within the walls of the gastrointestinal tract. When these cells penetrate the mucosal walls, the digestion and absorption of food, minerals and vitamins becomes compromised. The inflammatory response may become so severe that it causes increased intestinal vascular permeability, allowing protein loss by "leaking" into the intestinal lumen, unable to be reabsorbed. Canine IBD is a chronic, idiopathic, inflammatory disease with a pathogenesis that continues to be poorly understood. This case report will outline a severe form of IBD coupled with intestinal lymphangiectasia as well as the secondary effects of these two inflammatory processes (i.e. severe protein-losing enteropathy and cobalamin deficiency).

History and Presentation:

Lyla is an 8-year-old female, spayed Shetland Sheepdog that presented to MSU-CVM Emergency Service on 9/10/18 for suspected pulmonary edema and a history of pancreatitis. In late June of 2018, Lyla was diagnosed with pancreatitis after intermittent episodes of vomiting. After being hospitalized for two weeks at her primary veterinarian, she returned shortly after discharge for another episode of vomiting accompanied by loose stool. At that visit, a complete blood count and chemistry panel showed an elevated white blood cell count. She was placed on antibiotics. Lyla was scheduled for a recheck two weeks later and abdominal radiographs were performed. Diagnostics revealed thickened intestinal walls, per the primary veterinarian, and it was suspected to be IBD. Lyla was prescribed prednisone, which was dosed every other day, a vitamin, and a gastrointestinal-specific food. Unfortunately, Lyla's clinical symptoms were not resolving, and she presented again to her general practitioner for inappetence. A sample of blood was again collected and revealed hypocalcemia. She was placed on a calcium supplement and prescribed Cerenia for nausea. A few weeks later, Lyla presented yet again to her

veterinarian after no improvement. An abdominal ultrasound was performed and revealed thickened intestinal walls and fluid in her thoracic cavity. Her bloodwork showed a panhypoproteinemia, characterized by hypoalbuminemia (1.3 g/dL) and hypoglobulinemia (1.6 g/dL), hypocalcemia (iCa 4.2 mg/dL), hypocholesterolemia (26 mg/dL), mild anemia (HCT 36%), and mild stress leukogram. Lyla was then referred to MSU-CVM for further diagnostic work-up and treatment.

Upon presentation to MSU-CVM, Lyla was quiet, alert and responsive. During thoracic auscultation, no crackles or wheezes were appreciated, but she was noted to be tachypneic with an increased respiratory effort. Abdominal FAST (focused assessment with sonography for trauma) scan showed a mild amount of free fluid in multiple areas, while thoracic FAST scan revealed evidence of pleural effusion bilaterally with the right side being more severely affected. The remainder of her triage examination was within normal limits. Blood gas analysis revealed a mild hypocalcemia (iCa 0.91 mmol/L). An intravenous catheter was placed, and Lyla was hospitalized overnight with Vetstarch, a synthetic colloid, to help retain fluid within her vasculature as well as an anti-nausea medication, Cerenia.

On the morning of 9/11/18, FAST scans of her abdomen and thorax revealed no change in fluid accumulation. Her albumin was low at 1.2 g/dL, and she was started on clopidogrel to prevent thrombus formation. An abdominocentesis revealed a transudate. Lyla's urine analysis revealed no evidence of protein loss through the kidneys (urine protein-creatinine ratio 0.1), and a fecal flotation revealed no evidence of internal parasites. An abdominal ultrasound revealed a small nodule within the liver as well as hyperechoic foci within the mucosal layer of the small intestines. A bile acid test and an ammonia tolerance test were both abnormal. Due to the elevated results of the liver function tests, liver disease could not be ruled out. Lyla's coagulation panel was within normal limits, so it was decided to proceed with further investigation into her gastrointestinal disease by first performing a gastrointestinal endoscopy.

Lyla underwent general anesthesia on 9/12/18 for an upper and lower gastrointestinal endoscopy procedure. During endoscopy, her esophagus and small intestine were shown to be within normal limits. The small intestine revealed moderate dilated lacteals, moderate to severe duodenal mucosal irregularity as well as moderate mucosal irregularity in the ileum. The colon was visually within normal limits. Biopsy samples were then taken from her stomach, segments of duodenum and ileum and colon and submitted to the lab for histopathology. After discussing the possibility of hypocobalaminemia causing falsely elevated ammonia levels, Lyla was given an injection of cobalamin, and she was also started on calcitriol to aid in the absorption of calcium.

On the morning of 9/13/18, abdominal and thoracic FAST scans of Lyla's chest and abdomen showed slightly improved fluid accumulation. An appetite stimulant (mirtazapine) was initiated, as well as an additional anti-nausea medication (ondansetron). In the afternoon, her respiratory effort became labored, and her temperature increased to 103.2F. Her thoracic radiographs revealed no evidence of aspiration pneumonia (inflammation of the lungs caused by inadvertent inhalation of food or vomit material). Her intravenous catheter was suspected to be the cause of her elevated temperature, so it was removed. Her temperature returned to normal that night, and her appetite improved. Her stool remained soft. Her biopsy results were consistent with inflammatory bowel disease and lymphangiectasia. Immunosuppressive therapy (prednisone, cyclosporine) was begun. Lyla was discharged home the next day (9/14/18), although her albumin remained low at 1.1 g/ dl. However, after performing an ammonia tolerance test, her body’s ability to clear ammonia waste was appropriate, presumably after cobalamin supplementation.

The gastrointestinal panel results came back after discharge revealing a cobalamin deficiency as well as pancreatitis. Histopathology in all tissue sections examined lymphatic and/or lacteal dilation (lymphangiectasia). Lymphangiectasia coupled with the presence of moderate plasmacytic duodenitis,

ileitis, and colitis are highly suggestive of inflammatory bowel disease. No infectious agents were appreciated in the tissue samples submitted.

Pathophysiology/Anatomical Consideration:

Canine Inflammatory Bowel Disease (IBD) is an idiopathic chronic inflammatory process that can affect any part of the gastrointestinal tract. The small intestine is divided into three different sections beginning with the duodenum, jejunum, and ileum. These three sections of the small intestine are anatomically similar, but all have their own unique role in digestion. This extensive tubular structure is composed of four tissue layers, beginning with the outermost layer: tunica serosa, tunica muscularis, tunica submucosa and tunica mucosa. To better understand this disease process and its potentially catastrophic effect on the body, anatomy and physiology of the intestinal tract must be understood.

The entire surface of the small intestinal mucosa is composed of Crypts of Lieberkühn which lie between the intestinal villi. The crypts and villi are covered with goblet cells and enterocytes which secrete and reabsorb up to 2 liters of water and electrolytes per day.[2] The small intestine also plays a vital role in the absorption of water, nutrients, glucose, fat and ions such as sodium, chloride, calcium, iron, and bicarbonate. Typically, IBD will affect the innermost superficial layers of the intestinal tract, the mucosa primarily and submucosa, causing focal or diffuse thickening of the intestinal walls. Due to the chronic inflammatory response, infiltration of white blood cells compromises gastrointestinal function by decreasing absorption and secretion.

Although pathogenesis of inflammatory bowel disease is not completely understood, genetic, environmental and immunoregulatory factors are thought to play a vital role in the disease process.[1] The most common form of canine IBD is lymphocytic-plasmacytic enteritis. Protein-losing Enteropathy (PLE) is an uncommon complication of the effects of IBD on the intestinal mucosa, causing loss of albumin through the compromised gut wall. Albumin, a water- soluble protein, helps to maintain oncotic

pressure and plays an essential role in molecular transport. Even though canine inflammatory bowel disease causes an inflammatory response leading to leaky vasculature and mucosal exudation, the disease process has to be severe to cause marked hypoalbuminemia.[3] Mechanisms of protein loss through the gastrointestinal tract can be narrowed down to a physical or functional lymphatic obstruction, release of cellular mediators affecting vascular permeability and causing fluid leakage into tissues, and lastly, mucosal inflammation.[3]

Protein-losing enteropathy in canines is most commonly a sequela to IBD with or without, intestinal lymphangiectasia (IL), or both.[3] Primary lymphangiectasia is characterized as a disorder of the intestinal lymphatic system in which obstruction of the lymphatics causes distension and eventually, rupture of lacteals. This process leads to leakage of the lymphatic contents such as protein, lymphocytes and chylomicrons into the lumen of the small intestine.[4] Due to inflammation in the intestine, resorption of these contents cannot occur leading to a protein-losing enteropathy. Lymphangiectasia can also occur secondary to another disease process and results from lymphatic blockage, impairing drainage. However, since lymph can be a local tissue irritant, it can be difficult to histologically differentiate primary versus secondary IL and therefore challenging to diagnose.[3] Some of the laboratory abnormalities typically seen with IL include hypoalbuminemia, panhypoproteinemia, lymphopenia, hypocalcemia, and hypocholesterolemia.[8] PLE can be asymptomatic or if severe enough, can present as life-threatening effusions or lymphedema due to loss of lymphocytes, globulins, iron, calcium and other serum components leading to disruptions of immune defenses.[3] Thromboembolism is also a potential consequence of PLE.

Diagnostic Approach:

Since hypoalbuminemia can be due to either urinary, hepatic or gastrointestinal loss, it is essential for appropriate treatment to rule out and identify the source of protein loss. Diagnostic

approach to classify the cause of hypoalbuminemia involves performing a urine protein/creatinine ratio to identify pathologic proteinuria and a bile acid or an ammonia tolerance test to evaluate hepatic function. After ruling out protein loss due to renal and hepatic dysfunction, decreased albumin can most likely be attributed to loss through the gastrointestinal tract due to an inflammatory response.

The most common clinical signs associated with canine IBD may include weight loss, vomiting, and/or diarrhea. Since the disease process is patient specific, it is difficult to compare clinical signs, response to medical management, and patient prognosis to other cases. Numerous potential monitoring tools have been found useful in characterizing the severity of inflammation due to canine IBD including clinical scoring indices (Clinical Inflammatory Bowel Disease Activity Index and the Canine Chronic Enteropathy Clinical Activity Index), endoscopy and histopathology, abdominal ultrasound, serological markers (i.e. c-reactive protein, albumin, cobalamin and folate), and fecal markers.[5]

Inflammatory Bowel Disease is a diagnosis of exclusion by elimination of known causes of diarrhea as well as histology showing inflammatory infiltration of the intestinal mucosa, and architectural and epithelial changes.[4] Fecal flotation should be performed to rule out any intestinal parasite that could be residing in the intestinal tract. In stable patients with suspected IBD but a normal albumin, appetite, and weight, a stepwise diagnostic approach may be taken along with treatment trials and diet trials before extensive diagnostics. However, if these approaches fail or the patient is ill, hypoalbuminemic, or anorexic, diagnostics should not be delayed, but performed in lieu of treatment trials. A gastrointestinal panel is recommended to evaluate cobalamin levels, folate levels, pancreatic lipase immunoreactivity (PLI) and trypsin-like immunoreactivity (TLI). An abdominal ultrasound should be performed to evaluate the layers of the intestinal wall as well as intestinal contents and to search for any additional abnormal findings in the abdomen. Biopsy samples of the intestinal mucosa should be collected via endoscopy or obtaining full thickness intestinal biopsies during intraabdominal surgery. Although histologic evaluation is the gold standard for diagnosis of IBD, it is still difficult to accurately

define the severity of the disease process since the diagnosis is subjective and interpretation can vary between pathologists.[10] It is important to collect biopsy samples from multiple sites of the intestine to find inflammatory and neoplastic changes in the gastrointestinal tract. Histopathologic scoring systems evaluate the extent of fibrosis, villus stunting, crypt dilation, lacteal dilation, surface epithelial injury and lamina propria infiltrates.[10]

Treatment and Management:

The main goal in treatment of IBD is suppressing the inflammatory response and resolution of clinical signs. Initial treatment of mild cases of canine inflammatory disease involve elimination diets and antibiotics to distinguish IBD from dietary responsive enteropathy and antibiotic-responsive enteropathy. Instituting a novel protein or hydrolyzed diet has been shown to assist in resolution of clinical signs. Depending on the severity of lymphoplasmacytic enteritis (LPE) IBD, anti-inflammatories such as corticosteroids, more specifically prednisone, is usually the first choice in treating canine IBD. Budesonide, a non-halogenated glucocorticoid, has been suggested as an alternative treatment to prednisone, but further research has revealed fluctuating results and differences in outcome and efficacy.[8] If clinical disease is more severe, such as in cases of PLE due to IBD, additional immunosuppressants such as azathioprine, chlorambucil or cyclosporine are indicated. Probiotics have been shown to be effective in some cases with the thought that intestinal microbiota provide a defensive barrier, while helping digestion and giving nutritional support to enterocytes.[1] The use of additional antithrombotic medication is noted to be beneficial and debatably crucial while treating dogs with PLE, since a small percentage of dogs with PLE develop thromboembolism (TE).[3] Although further research suggests TE is occurring more often than believed and have been diagnosed more frequently after further investigation and post-mortem. Comparatively in human medicine, the pathogenesis of TE developing due to PLE is not completely understood but it most likely a multifactorial process, with the loss of anti-thrombin playing a significant role.[11] Placing dogs on antithrombotics, such as clopidogrel,

can be beneficial but prolonged treatment has been recommended since dogs that are noted to be in remission of PLE can die suddenly from TE,[3] more commonly pulmonary thromboembolisms.[11] If the patient responds clinically, it is important to continue therapeutic treatment for an additional 2-4 weeks to ensure that improvement is in response to the initial therapy.[4] Once the disease process is in remission, slowly reducing one therapy at a time a every two to four weeks is recommended.

For cases of IBD with lymphangiectasia, treatment involves instituting an ultra-low-fat diet, in addition to the immunosuppression and other treatments listed above. Although most clinical cases of lymphangiectasia require glucocorticoid administration, diet plays a crucial role in resolution of clinical signs. Dietary fat restriction has shown to be an effective treatment in dogs that have been unresponsive to steroid therapy or have relapses of hypoalbuminemia with clinical signs and symptoms when doses of prednisone are reduced.[8]

Once the intestinal inflammatory process is managed with diet and medical therapy, the panhypoproteinemia should start to improve. A recent study showed clinical outcomes of patients with PLE are variable. However, the majority of the dogs that presented for PLE had prolonged survival despite the severity of the disease process and clinicopathological findings at initial diagnosis.[9] Therefore, it may be difficult to give an accurate prognosis to patients that have protein-losing enteropathy regardless of the severity of clinical signs.

Discussion and Case Outcome:

Since Lyla's protein levels were so low, the main attributing factor was thought to be due to lymphangiectasia. During her hospitalization, she was offered a few low-fat, hydrolyzed diets and sent home with Purina Prescription Diet EN Low fat canned and dry food as well as HA (hydrolyzed diet) canned food. Upon discharge, Lyla was sent home with prednisone (20 mg SID), to suppress the immune system and decrease inflammation, as well as cyclosporine (50 mg BID), an immunosuppressive agent.

She was prescribed omeprazole (10 mg SID) to be continued for an additional two weeks and to continue her antibiotic course of metronidazole (175mg BID) for the next 5 days. Her owners were also instructed to continue administration of calcitriol and clopidogrel, an anti-platelet medication, until her scheduled recheck examination. Lyla was prescribed mirtazapine as an appetite stimulant, as needed and Cerenia for potential nausea. It was recommended to continue the cobalamin injections once weekly for 6 weeks, then one dose 30 days later and to finally re-test her 30 days after her last injection to assess her cobalamin levels. Lyla was scheduled for a recheck examination with her primary veterinarian 6 days after being discharged to receive an additional subcutaneous cobalamin injection and to check her ionized calcium levels. Her owners were instructed to return to MSU-CVM two weeks later to re-evaluate her blood work and see how she was responding to her current medical therapy.

Lyla presented to MSU-CVM two weeks later for her recheck examination where her owners were concerned with lethargy, weight loss and inappetence at this time. A sample of blood was collected and submitted for a complete blood cell count and chemistry panel. Lyla's bloodwork revealed a mild leukocytosis (22.9 K/ul), a mild anemia (31%), hypoproteinemia (5.2 g/dl), and hypomagnesemia (1.4 mg/dl). Several diet trials were performed in hospital, and she was noted to have a robust appetite. Since her owners were having trouble getting Lyla to eat, boiled chicken was eventually added to her diet without exacerbation of clinical signs. Numerous low-fat novel protein and hydrolyzed diets were tried once again in the clinic and Lyla was sent home with Hill's D/D dry and canned food to try at home. Lyla was continued on prednisone and cyclosporine at the same dose that was previously prescribed and mirtazapine and Cerenia as needed. We recommended rechecking Lyla's albumin level two weeks after presenting that day and if still exhibiting clinical signs of IBD, to measure her levels of cyclosporine to ensure she is being appropriately medically managed.

Follow-up a month later with her primary veterinarian revealed that Lyla was doing wonderfully with her irregular values on bloodwork normalizing (HCT: 45, Globulins: 4.3, Albumin: 2.9) but a

cholesterol of >500 and bilirubin was noted to be around 1.0. Lyla had a resolution in clinical signs and was noted to be gaining weight. At that time, it was suggested to decrease her prednisone dose from 20 mg once daily to 15 mg once daily and have her re-assed in two weeks to check her albumin levels and ultrasound to monitor for the development of a mucocele.

In this specific case report, it should be noted that cobalamin played an essential role in some of the confounding abnormalities in Lyla's diagnostic work-up. Cobalamin (B12) is an essential vitamin that is absorbed in the ileum of the small intestine and is required for cellular metabolism is the body. It has been suggested that chronic intestinal inflammation impairs the expression of cobalamin intrinsic factor receptors in the ileum[7], making low levels of cobalamin a common finding and indicative of disease of the distal intestinal tract. Since cobalamin is needed for most major metabolic pathways, cobalamin deficiency will negatively affect numerous organ systems, but the extent of its impact is not completely understood. A more recent study by McLauchlan et al, describes methylmalonic aciduria secondary to cobalamin deficiency. This individual case report goes on to describe elevation in post-pranial bile acids which suggested hepatic dysfunction as well as hyperammonemia on initial presentation.[6] However, 24 hours after cobalamin administration, post-pranial bile acids and ammonia returned to normal which may signify that cobalamin may have been a contributing factor. Keeping this in mind and with no other evidence of hepatic dysfunction, Lyla was given a cobalamin supplement while waiting for the results of her GI panel, and no further liver diagnostics were pursued while awaiting response to cobalamin. Post-prandial bile acids and ammonia tolerance testing were indeed within normal limits 24 hours after cobalamin administration.

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