Don’t Let the Sludge Get You Down

A Case of Canine Gallbladder Mucocele

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Introduction:

Gallbladder mucocele is a mucus-filled dilation of the gallbladder that is secondary to dysfunction and hyperplasia of mucus-secreting cells within the gallbladder mucosa. Often the gallbladder becomes so distended that mucus cannot be excreted from the bile duct, leading to pressure necrosis or subsequent risk of gallbladder rupture.[1,2,3] Recent years have shown an increase in the frequency of canine gallbladder mucocele diagnoses in veterinary medicine. Middle to older aged dogs, averaging 9 years of age, are predisposed with no current sex predilection. Typical breeds predisposed include Shetland sheepdogs, Cocker Spaniels, Miniature Schnauzers, and other small dog breeds. Most patients with gallbladder disease are asymptomatic for years, or exhibit clinical signs that are often non-specific including vomiting, lethargy, anorexia, abdominal distention, and polyuria-polydipsia. The use of ultrasound enhances a clinician's ability to monitor and make presumed diagnoses based on non-specific clinical signs.[8] Treatment for gallbladder mucocele is case and clinician dependent, and includes-medical management or surgical management via a cholecystectomy. Treatment for gallbladder mucocele patients provide an excellent long-term prognosis in the majority of cases.[1,7]

This case report describes a scenario in a 14-year-old, neutered male Dachshund that developed a gallbladder mucocele with previously diagnosed endocrinopathies. There are reports that propose endocrinopathies such as hyperadrenocorticism and hypothyroidism may play a role in gallbladder disease, but this correlation has not been thoroughly researched.[5]

History and Presentation:

Teddy, a 14-year-old, neutered male Dachshund, presented to Mississippi State University College of Veterinary Medicine (MSU-CVM) Internal Medicine Department on July 3, 2018, for an ACTH (adrenocorticotropic hormone) stimulation test, blood glucose curve, and boarding. Teddy was diagnosed with IVDD (intervertebral disc disease) in the cervical neck in 2014, which was medically managed. Teddy was diagnosed with diabetes mellitus in 2014 and was placed on Vetsulin injections (10 units twice daily). Approximately 1 month after the diabetes mellitus diagnosis, Teddy developed bilateral cataracts, which were corrected with surgery at that time. Teddy developed dry eye and glaucoma which was managed with cyclosporine/tacrolimus drops and latanoprost ophthalmic solution. Teddy was diagnosed with hyperadrenocorticism in 2017 and was managed on Vetoryl 10mg tablet twice daily. Teddy had a familial history of hyperadrenocorticism, and a long-term history of elevated ALP (alkaline phosphate). Teddy had a history of intermittent urinary tract infections, which began shortly after diabetes diagnosis. Teddy's owner reported that he does not exhibit excessive drinking or urination, but he had become polyphagic and was more tired since the initial diagnosis of hyperadrenocorticism. Teddy was up-to-date on yearly vaccinations and flea/heartworm preventative. Teddy was housed primarily indoor with one other dachshund.

On presentation, Teddy was bright, alert, and responsive. Teddy weighed 9kg with a body condition score of 4/9. His vital parameters were within normal limits with a temperature of 100.4°F, a pulse of 148 beats per minute, and a respiratory rate of 36 breaths per minute. Teddy had a normal hydration status, with pink and moist mucous membranes and a capillary refill time of less than 2 seconds. Thoracic cavity auscultations revealed a grade II/VI left apical systolic murmur, but overall normal bronchovesicular sounds were heard in all lung fields.

Teddy had pseudophakia in the lens capsules of both eyes, attributed to his previous cataract surgery. Oral exam revealed several dental extractions, along with progressive dental disease and halitosis. Abdominal palpation was unremarkable and displayed a pot-bellied appearance. Overall Teddy's skin was flaky and had a thin hair coat. Several freely movable soft subcutaneous masses were noted along the ventral aspect of the body with the largest one being in the left axillary region. The remainder of his physical exam was within normal limits.

An initial workup on July 3, 2018, which included a complete blood count, chemistry panel, coagulation panel, urinalysis and urine culture/sensitivity were performed. Results revealed that the complete blood count and coagulation panels were unremarkable, chemistry panel revealed moderate elevated blood glucose (328 mg/dl), severely elevated alkaline phosphate (1560 U/L), mild hyperkalemia (6.37 mmol/L), and mild hypercalcemia (13.6 mg/dl). The urinalysis revealed 2+ glucose, few calcium oxalate crystals, but negative ketones. Urine culture and sensitivity came back as no growth over 48hrs. Teddy had thoracic and abdominal radiographs performed, revealing moderate bronchial lung changes, mild left atrial enlargement, liver enlargement, spleen enlargement, and cystolithiasis. Diagnostic abdominal ultrasound showed bilaterally enlarged adrenal glands, liver enlargement, gallbladder sludge with progressive mucocele formation, as well as, splenic nodules, left renal cortical infarct, and few small bladder stones within the urinary bladder. Due to the gallbladder mucocele progression and after speaking with Teddy's owners it was elected to continue to board Teddy through the July 4th holiday. Then on July 5,2018, Teddy was transferred to MSU surgery department and was scheduled for cholecystectomy surgery, along with a cystotomy to address his chronic cystolithiasis.

Pathophysiology:

Gallbladder mucocele is a common cause of extrahepatic biliary obstruction in dogs and is the most common diagnosis resulting in need for surgical treatment. Gallbladder mucoceles are characterized histologically by evidence of hyperplasia of mucus-secreting glands within the gallbladder mucosa, which result in abnormal accumulation of thick mucus within the lumen. Abnormal mucosal cells may be due to a primary defect, or may be the result from endogenous or exogenous substances acting on gallbladder epithelium, or due to a decrease in motility.[3] Mucins, play a major role in the development of gallbladder mucoceles. Mucins are a family of polysaccharides secreted by mucosal epithelial cells of the gallbladder, stomach, intestines, and other organs. Mucins act like surfactant and have a mucoprotective role by preventing self-digestion of mucosal epithelium by digestive secretions.[6] The exact etiology is not completely understood. There are many suspected causes that make the formation of a gallbladder mucocele complex and multifactorial.

The most common suspected cause of gallbladder mucocele formation is altered function of gallbladder wall contractility. There is an increased number of cases seen where patients may have one or more of the following: hyperadrenocorticism, hypothyroidism, and pancreatitis.[2,1] One study found no statistical significance associated between the presence of gallbladder mucocele along with diabetes mellitus, but further research is still being performed.[5] It remains unclear how cholestasis and biliary sludge in dogs is associated with development of gallbladder mucocele, but it is likely a secondary reason for formation.[8] Many studies indicate that the principal component of gallbladders with biliary sludge and or gallbladder mucoceles is mucins. This suggests that mucins are highly likely involved in the pathogenesis of not only gallbladder

mucoceles but also biliary sludge. Therefore, gallbladder mucocele and biliary sludge may not be independent of each other, but in fact represent a continuous disease.

One study found that dogs previously diagnosed with hyperadrenocorticism were 29 times more likely to have findings of a gallbladder mucocele and represented 21% of the gallbladder mucocele population in that study. It is thought that the alteration of bile acid causes cytotoxicity in the hypercortisolemic states or concurrent immunosuppression causing gallbladder dysfunction. In hypothyroid dogs the use of thyroxine allows relaxation of the sphincter of Oddi, at the major duodenal papilla, which is thought to cause increased tonicity of the sphincter and result in biliary stasis. Thyroxine increases the mucus production, risk of developing a gallbladder mucocele, and the contact time within the gallbladder leading to irritation of the gallbladder wall. Bloodwork may reveal hypertriglyceridemia or hypercholesterolemia associated with formation of dyslipidemia. Dyslipidemia seems to be associated with the development of gallbladder mucocele. This is likely due to an increased conversion of cholesterol into bile acids as part of a catabolic escape pathway.[3,8]

Another proposed theory suggests that an insertion gene mutation in exon 12 of canine adenosine triphosphate-binding cassette (ABCB4) is a relative risk factor for development of gallbladder mucocele in Shetland sheepdogs.[4] The gene mutation results in the elimination of more than 50% of functional proteins (phospholipids and phosphatidylcholine). ABCB4 functions as a phospholipid translocator on the canalicular membrane of the hepatocytes. Proper function of ABCB4 is critical for maintaining hepatobiliary homeostasis.[4] The gallbladder epithelium in heterozygous dogs that harbor ABCB4 undergoes greater exposure to non-neutralized bile salts than in wildtype dogs, resulting in greater mucin secretion, mucinous hyperplasia, and eventually mucocele formation. Chronic injury to the epithelial lining of the

biliary system is due to hypersecretion of mucin, which is the physiological response of any epithelial injury. Therefore, association of ABCB4 with gallbladder mucoceles in dogs represents an important area for advancement in understanding, diagnosing and treating the disease. [4,8]

Diagnostic Approach/ Considerations:

Patients with gallbladder mucocele may present asymptomatic or symptomatic. Clinical signs are non-specific including vomiting, lethargy, anorexia, abdominal distention, and polyuria-polydipsia. Further workup should be pursued with complete blood count, chemistry, coagulation plan, abdominal radiographs, and most importantly abdominal ultrasound. Complete blood count may reveal anemia, leukocytosis, and/or monocytosis. Serum chemistry often demonstrates increased liver enzymes, azotemia, hyperbilirubinemia, hypertriglyceridemia, hypercholesterolemia, and even hypoalbuminemia if ruptured biliary tree is present with abdominal peritonitis.[2] Coagulation panels are usually normal unless more severe disease is present or gallbladder rupture has occurred.[3] The main finding in abdominal radiographs is hepatomegaly, since the gallbladder is usually not identified. Often the diagnosis is discovered during abdominal ultrasound when examining the patient for other health reasons. Abdominal ultrasound findings are characterized by gallbladder distention, thickened gallbladder wall, and moderate amounts of biliary sludge with the appearance of an intraluminal mass that does not move. Additionally, intraluminal echogenic membranes are present, described as stellate or striated pattern, like the appearance of a sliced kiwi fruit. Ultrasound is a highly reliable diagnostic tool for the identification of gallbladder mucocele or gallbladder rupture. The sensitivity of ultrasound for gallbladder mucocele/rupture was 85.7% which compares favorably to the reported sensitivity rate of 70% in humans in one study.[7] Another study suggested two

other diagnostic tests such as gallbladder ejection fraction index and hepatobiliary scintigraphy- which are helpful in determining bile duct patency and gallbladder dysmotility.[6] These test results provide a better understanding of the etiology and pathology of gallbladder mucoceles due to the increased exposure time of highly concentrated bile salts.[8] It is recommended that dogs diagnosed with a gallbladder mucocele be screened for concurrent endocrinopathies if clinical suspicion is present. A heightened degree of suspicion of gallbladder mucocele should be present in dogs with pre-existing hyperadrenocorticism or hypothyroidism.[5]

Majority of gallbladder mucocele cases are taken to surgery for removal of gallbladder via cholecystectomy, as well as to collect multiple biopsy samples from the gallbladder and liver. Histopathology results show all gallbladders have hyperplasia of mucosal mucus-secreting glands and abnormal accumulation of mucus within the gallbladder lumen, confirming the diagnosis of gallbladder mucocele. The affected mucus-secreting glands are severely dilated with mucus within the gallbladder lumen. In some gallbladders the mucosa will contain cysts lined by a single layer of epithelial cells surrounding a mucus-filled lumen. In more severe cases, transmural ischemic necrosis may lead to gallbladder rupture at time of surgery. Liver biopsy results showed mild to moderate portal hepatitis and fibrosis with presence of bile duct proliferation.[7]

Treatment and Management:

The approach to treatment and management of gallbladder mucocele depend on the presence of clinical signs and routine monitoring. The two types of treatment are medical or surgical. It is recommended that any dog exhibiting advanced clinical signs and symptoms of gallbladder mucocele have a cholecystectomy performed. Cholecystectomy remains the treatment of choice for a gallbladder mucocele in a patient that is at high risk of ruputuring.[3, 8]

Medical management can be considered for dogs that are asymptomatic. Owners must be made aware that asymptomatic cases may eventually develop into an acute clinical emergency should the disease continue to progress to extrahepatic biliary obstruction or gallbladder rupture. The cornerstone medical therapy includes choleretics, hepatoprotectants, and low-fat diet. Ursodeoxycholic acid (ursodiol) is a naturally occurring hydrophilic bile acid that functions as a choleretic and hepatoprotectant at 10-15 mg/kg orally, as a single dose or divided into two doses per day. There is also evidence that ursodiol upregulates phospholipid transporters in bile canaliculi and may help resolve mucoceles. The effects of long-term use of ursodiol treatment is unknown.[3] Before placing patients on ursodiol, be sure that there is no evidence of biliary obstruction because this medication may risk gallbladder rupture. S-adenosylmethionine (SAMe) is a naturally occurring precursor of cysteine that is essential in the production of the antioxidant glutathione, serves as a hepatoprotectant at 8-20 mg/kg orally, as a single dose once daily on an empty stomach. Lastly, a low-fat diet is helpful, especially in animals with dyslipidemia. Patients with concurrent endocrinopathies must be treated and monitored appropriately. Most medically managed cases require follow-up visits every 2-4 weeks for abdominal ultrasound, complete blood count, and chemistry. At any point that progression of disease and worsening of clinical signs occurs, immediate surgical invention is warranted.[8,9]

Surgical management is the standard of care for a symptomatic patient. Because the risk of gallbladder rupture always exists and is associated with increased perioperative morbidity (21.7-40%), it is recommended that surgery not be postponed for an extended period. Antibiotics should be started before surgery and may need to be continued for weeks after surgery. During surgery antibiotics are administered intravenously, immediately prior to surgery, every 2 hours during anesthesia. Antibiotics are most effective in preventing

postoperative infections when adequate blood levels are present throughout surgery. The decision to continue antibiotics beyond surgery is up to the clinician and based on the individual patient's status. Ideally, antibiotic selection would be based on culture and sensitivity, but empirical therapy with ampicillin and enrofloxacin has been used.[3,6] Preoperative complete blood count, chemistry, coagulation panel, and urinalysis are recommended in all cases.

It is recommended that the patency of the common bile duct is confirmed prior to cholecystectomy, via manual normograde expression of the gallbladder or retrograde catheterization of the common bile duct through a duodenal enterotomy.[8] The gallbladder is freed from the liver by blunt dissection and using Metzenbaum scissors to cut the fibrous bands attaching the gallbladder to the liver. Once the gallbladder is freed, the biliary tree must be flushed prior to ligation of the cystic duct to remove residual biliary sludge or inspissated bile to minimize the risk of post-operative biliary obstruction. The cystic duct and artery should be double clamped and ligated using 2/0 or 3/0 PDS (polydioxanone suture). Once the gallbladder is removed, tissue is saved for histopathology. Liver biopsy is recommended, as well as an aerobic/anaerobic culture of gallbladder contents.[8,9]

Case Outcome:

Teddy was transferred to MSU-CVM surgery department on July 5, 2018, and was scheduled for cholecystectomy surgery, along with cystotomy to address his chronic cystolithiasis. At time of induction Teddy received the first dose of cephazolin intravenously and every 90 mins throughout surgery. During surgery it was confirmed that the gallbladder was very descended but not at the point of rupturing. Surgery was performed with no complications. Following surgery, biopsies of the gallbladder, liver, and spleen were taken for histopathology, along with liver anaerobic/aerobic culture and urinary bladder stones for evaluation. Overnight

in ICU, Teddy had an increase in respiratory effort with crackles auscultated on the right thoracic region. He also appeared to remain painful with a Glasgow Pain Score of 6/24. At that time a 5mcg/kg/hr bolus of fentanyl was given along with an increase on his CRI at 4mcg/kg/hr. On July 6th, thoracic radiographs were performed to evaluate Teddy's lung fields for aspiration pneumonia. Thoracic radiographs revealed no radiographic evidence of aspiration pneumonia.

During his recovery, he developed an increased respiratory rate and lung crackles resolved. On July 8, 2018, Teddy was transferred out of ICU to continue recovery in wards. His medications were switched from intravenous to orals, which consisted of Tylenol 4 and maropitant. Teddy's surgical biopsy histopathology reports confirmed the diagnosis of gallbladder mucocele. The gallbladder had multiple sections characterized by abundant luminal pale amphophilic material. The liver contained vacuolar hepatopathy with lipogranulomas and equivocal lobular hyperplasia. The spleen contained splenic nodular lymphoid hyperplasia and myeloid metaplasia. Urinary stones were confirmed as calcium oxalates. Teddy was sent home July 9, 2018 with instructions to continue Vetoryl (10mg tab twice daily), Vetsulin (13units twice daily), and eye drops as previously prescribed. Teddy was to finish out the remainder of Tylenol 4 and maropitant until gone and return in 2 weeks for recheck of surgical incision, recheck ACTH stim levels, and to perform a blood glucose curve to better regulate his diabetes mellitus.

On July 24, 2018, Teddy returned to MSU-CVM Internal Medicine department for ACTH stimulation test, blood glucose curve, check incision site, and boarding. His's owner reported that Teddy had been doing well at home but still had a poor appetite and seems to still be losing weight. Teddy's incision had healed appropriately, and skin staples were removed. The results of his ACTH stimulation test revealed that his hyperadrenocorticism was regulated appropriately. His pre-medicated blood sample was 5.1 ug/dl, then 1-hour post cortisol sample

was 5.2 ug/dl and post cortisol sample was 2.7 ug/dl. Blood glucose results on July 25th, revealed that the glucose was too low to give insulin. He was monitored throughout the day, and half of his normal insulin dose (7.5 units) was given. Blood glucose concentrations were monitored for the next day to make sure that he did not become hypoglycemic. Due to Teddy's unregulated diabetes he was a candidate for a new blood glucose monitoring device called a Freestyle Libre sensor. This monitoring device is used to obtain a more accurate long-term glucose curve in diabetic patients. At this visit it was recommended to lower Teddy's insulin dose to 5 units twice daily. The owner was instructed how to use the new glucose monitoring device and it was stressed to not change the dose of Vetsulin without consulting MSU-CVM Internal Medicine department first. It was instructed for Teddy to return in 11 days to remove the Freestyle Libre device and analyze the results.

On August 20, 2018, Teddy returned for dental prophy and a new Freestyle Libre glucose monitoring device. The owner reported that Teddy had been drinking and urinating more frequently and still remained tired throughout the day. Over the past month, Teddy's glucose doses were changed based on the readings from his Freestyle Libre. On July 28, 2018, Teddy was PU/PD (polyuric/polydipsic) and the sensor was reported glucose readings above 350 mg/dl. Vetsulin dose was increased to 7 units. On August 2, 2018, Teddy remained PU/PD and Vetsulin dose was increased to 9 units. After removal of the Freestyle Libre at the rDVM, the owner increased Vetsulin dose to 10 units. Owner reported that even though Teddy was still PU/PD he had improved over the last month with increased Vetsulin dosages. Teddy had complete blood count, chemistry, and urinalysis performed prior to undergoing anesthesia for his dental prophy on August 21st. Teddy had six teeth extracted due to his severe stage IV periodontal disease. Chemistry revealed severely elevated hypercalcemia compared to his

previous blood work which warranted thoracic radiographs, abdominal radiographs, and a malignancy profile to rule-out an etiology for hypercalcemia. Teddy was sent home on August 22nd, with Clavamox 125mg (1 tab twice daily for 10 days) and Tylenol 4 60mg (1/4 tablet every 8hrs for 5 days). To date, Teddy was receiving 11 units of Vetsulin twice daily to regulate his diabetes mellitus. The results of the malignancy panel confirmed a diagnosis of primary hyperparathyroidism. This visit concluded the relevant follow-up for Teddy's gallbladder mucocele procedure, but Teddy continued to be quite the internal medicine case.

On September 20, 2018, Teddy returned to MSU-CVM Internal Medicine to have parathyroid ultrasound in preparation for a possible parathyroid mass removal. Parathyroid gland ultrasound revealed two suspected nodules cranial to the right thyroid gland. Echocardiogram revealed clinical signs of chronic mitral valve disease (ACVIM stage B2, mild-moderate regurgitation with valve prolapse). September 24th, Teddy had a right parathyroidectomy and was monitored for post-operative hypocalcemia. Since then Teddy had been seen for routine dentals, rechecks to control diabetes mellitus via Freestyle Libre monitoring, and continued monitoring of ACTH levels for control of hyperadrenocorticism. On January 14, 2019, Teddy returned to MSU-CVM Internal Medicine Department where he was diagnosed with chronic kidney disease IRIS Stage 2. Due to Teddy's comorbidities and declining quality of life, Teddy's owners elected to humanely euthanize him to go rest in his forever home on January 20, 2019.

Conclusion:

The short- and long-term survival for biliary surgery is roughly 66%. Most mortalities occur within the first 2 weeks after surgery, with long-term survival beyond that point being excellent.[8] Gallbladder rupture is common; however, prompt surgical intervention following

gallbladder rupture can produce excellent results.[7] From the results of current literature and studies, a good prognosis is reported for intact gallbladder mucocele removals, such as Teddy's case.[1] With gallbladder mucocele becoming an increasingly common cause of extrahepatic biliary disease in dogs, it is essential that clinicians remember to have it on their differential diagnoses list for suspect gallbladder disease.

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