Introduction

Over the past decade, gallbladder mucocoeles (GBM) have become a frequently recognised cause of extrahepatic biliary (EHB) disease in canines (Aguirre et al. 2007; Quinn & Cook 2009). This condition is rarely diagnosed in cats, with only two cases reported in the recent literature (Bennett et al. 2007; Woods et al. 2012).

Gallbladder mucocoeles are defined as an abnormal accumulation of inspissated, semi-solid bile and/or mucus within the gallbladder lumen (Mesich et al. 2009; Norwich 2011). The result is macroscopic distension of this organ with green-black gelatinous material that may extend throughout the biliary tree, causing variable degrees of EHB obstruction (Center 2009; Mesich et al. 2009). When EHB obstruction develops, gallbladder distension often leads to necrosis of the gallbladder wall and eventual rupture, with subsequent peritonitis (Worley, Hottinger & Lawrence 2004).

Its distinctive ultrasonographic appearance combined with historical, physical examination and serum biochemistry findings makes its diagnosis fairly easy (Center 2009; Kook et al. 2012). At the time of diagnosis, dogs are frequently suffering from concurrent problems that include pancreatitis, hyperlipidaemia, corticosteroid excess, hypothyroidism, protein-losing nephropathy, diabetes mellitus, cholestasis and gallbladder dysmotility (Aguirre et al. 2007). The mainstay of treatment is surgery, but medical management of selected cases has also been described (Quinn & Cook 2009).

Owing to its typical presentation, it is unlikely that the condition was previously misdiagnosed and its increasing incidence makes this an emerging syndrome in veterinary medicine.

Anatomy

The gallbladder is a pear-shaped organ located in the right cranial abdominal quadrant. It is situated in the gallbladder fossa of the liver between the quadrate and right medial liver lobes. It consists of a fundus, body and neck that attaches, via a short cystic duct, to the common bile duct (Center 2009; Quinn & Cook 2009). The gallbladder wall consists of five histologically distinct layers. From the innermost these include the epithelium, submucosa (consisting of the lamina propria and tunica submucosa), tunica muscularis externa, tunica serosa (outermost layer covering the aspect of the gallbladder facing away from the liver) and tunica adventitia.
Review Article

Predisposing factors and aetiopathogenesis

The aetiology of GBM is incompletely understood, but is suspected to be complex and multifactorial (Norwich 2011).

Certain endocrinopathies (e.g. hyperadrenocorticism and hypothyroidism but not diabetes mellitus) may be implicated in the development of GBM (Meler & Pressler 2010). One study found that dogs previously diagnosed with hyperadrenocorticism were 29 times more likely to have findings of GBM, and comprised 21% of the GBM population in that study (Mesich et al. 2009). A separate study (n = 30) found 23% of dogs with GBM had hyperadrenocorticism (Pike et al. 2004).

In an attempt to create a GBM model, beagles received twice daily exogenous steroid administration (8.5 mg/kg hydrocortisone, q 12 hours) for 84 days to recreate hyperadrenocorticism (Kook et al. 2011, 2012). No significant differences were noted between treated dogs and controls, with sludge visible in the gallbladders of both groups. The most significant outcome of this experimental study was that the iatrogenic hypercortisolaemic state caused a reversible shift in bile salt composition towards an increased concentration of cytotoxic, hydrophobic, unconjugated bile acids. It has been demonstrated that these hydrophobic bile salts act as a mucin secretagogue in canine gallbladder epithelial cell cultures (Klinkspoor et al. 2002). From these experimental studies it can be postulated that alterations in bile acid cytotoxicity in the hypercortisolaemic states may be the cause of gallbladder dysfunction. Other hypotheses include an increased risk for the development of bacterial cholecystitis (as a result of concurrent immunosuppression) and alterations in gall bladder motility that may predispose to the development of GBM (Mesich et al. 2009).

Hypothyroid dogs were three times more likely to have GBM compared to euthyroid animals, but an observational bias may have resulted from dogs with confirmed GBM having an increased likelihood of being tested for hypothyroidism than control animals (Mesich et al. 2009). Thyroxine allows relaxation of the sphincter of Oddi, at the major duodenal papilla, of humans and pigs (Laukkanen et al. 2002). Likewise, if it is deficient or absent, it is thought to cause increased toxicity of the sphincter and resultant biliary stasis. The increased contact time allows concentration of bile, leading to irritation of the gallbladder wall and increased mucous production. Thyroxine also affects bile acid composition, which may play a role in the development of GBM in hypothyroid dogs (Meler & Pressler 2010; Mesich et al. 2009).

Dyslipidaemias (due to hypothyroidism, hyperadrenocorticism and idiopathic hyperlipidaemia) seem to be associated with the development of GBM. This may be due to an increased conversion of cholesterol into bile acids as part of a catabolic escape pathway (Kook et al. 2012).

Interestingly, an insertion mutation in exon 12 of canine adenosine triphosphate-binding cassette (ABCB4) may be a relative risk factor for the development of GBM in Shetland sheepdogs (Cullen 2009; Mealey et al. 2010). This mutation eliminates more than 50% of the functional protein. ABCB4 functions as a phospholipid translocator on the canalicular membrane of hepatocytes. In its absence, the concentration of phospholipids in the biliary lumen decreases, which increases the cytotoxicity of bile salts. The mutation is believed to be inherited in a dominant fashion with incomplete penetrance (Mahaffey 2011; Mealey et al. 2010).

Other steroid hormones (e.g. progesterone) result in concentration-dependent inhibition of gall bladder motility. Cholestasis may predispose animals to the development of GBM by increasing the contact time and allowing bile to become concentrated. This results in the irritation of the gallbladder wall and increased mucous production (Mesich et al. 2009; Quinn & Cook 2009).

Finally, the significance of biliary sludge in dogs and its association with the development of GBM remains unclear, but it is unlikely that the disease develops from normal bile without intermediate microprecipitate formation (Kook et al. 2012; Quinn & Cook 2009; Tsukagoshi et al. 2012).

Based on the current literature alone, it is apparent that many predisposing factors have been identified, but the aetiopathogenesis remains speculative in this species.

Diagnosis

A summary of the signalment, clinicopathologic changes and bacteriology associated with gallbladder mucocoeles in dogs and cats is provided in Table 1.

Signalment

Older small- to medium-breed dogs seem to be predisposed (Norwich 2011). An average age of 9.1 years was found upon reviewing the current literature, but no sex predilection has been established (Aguirre et al. 2007; Besso et al. 2000; Choi et al. 2014; Crews et al. 2009; Malek et al. 2013; Mayhew,
TABLE 1: A summary of the signalment, clinicopathologic changes and bacteriology associated with gallbladder mucocoeles in dogs and cats generated by careful consideration of the mentioned reference list.

<table>
<thead>
<tr>
<th>Description</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of animals reported in the literature</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dogs</td>
<td>400</td>
<td>-</td>
</tr>
<tr>
<td>Total dogs where breed described</td>
<td>317</td>
<td>-</td>
</tr>
<tr>
<td>Cats</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Breeds</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Shelties</td>
<td>79</td>
<td>24.90</td>
</tr>
<tr>
<td>Cocker spaniels</td>
<td>56</td>
<td>17.60</td>
</tr>
<tr>
<td>Mixed breed</td>
<td>42</td>
<td>13.20</td>
</tr>
<tr>
<td>Miniature schnauzers</td>
<td>16</td>
<td>5.00</td>
</tr>
<tr>
<td>Bichon Frise</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>Miniature/toy poodles</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>Beagles</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Dachshund</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Pomeranians</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>Yorkshire terriers</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>Maltese poodle</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Shih-tzu</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>German shepherd dog</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Chihuahua</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Labrador retriever</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Min-pin</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Collie breeds</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Lhasa apso</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Shiba inu</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Bassett hound</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Border terrier</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Cock-a-poo</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Soft-coated wheaten terrier</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Australian shepherd, Bernese mountain dog, Cairn terrier, golden retriever, Havanese, Jack Russell terrier, Keeshond, Norwich terrier, Pekingese, Siberian husky</td>
<td>1 of each</td>
<td>-</td>
</tr>
<tr>
<td>Sex (where reported)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>178</td>
<td>53.60</td>
</tr>
<tr>
<td>Male</td>
<td>154</td>
<td>46.40</td>
</tr>
<tr>
<td>Mean age (years old)</td>
<td>10.2</td>
<td>-</td>
</tr>
<tr>
<td>Clinical signs (where reported)</td>
<td>166</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>115</td>
<td>69.30</td>
</tr>
<tr>
<td>Lethargy</td>
<td>73</td>
<td>44.00</td>
</tr>
<tr>
<td>Anorexia</td>
<td>70</td>
<td>42.20</td>
</tr>
<tr>
<td>Abdominal pain/discomfort</td>
<td>32</td>
<td>19.30</td>
</tr>
<tr>
<td>Icterus</td>
<td>27</td>
<td>16.30</td>
</tr>
<tr>
<td>PU/PD</td>
<td>13</td>
<td>7.80</td>
</tr>
<tr>
<td>Symptomatic vs. asymptomatic (where reported)</td>
<td>122</td>
<td>-</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>87</td>
<td>71.30</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>35</td>
<td>28.70</td>
</tr>
<tr>
<td>Gallbladder (GB) rupture</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cases where GB ruptured</td>
<td>45</td>
<td>27.80</td>
</tr>
<tr>
<td>Total number of GBM cases where GB rupture reported</td>
<td>162</td>
<td>-</td>
</tr>
</tbody>
</table>

Clinicopathologic findings

The results of a complete blood count are usually unremarkable with leukocytosis evident in 46.9% of cases. The leukocytosis can be characterised by a left shift neutrophilia (regenerative or degenerative) (Worley et al. 2004). Serum biochemistry reveals increased liver enzymes, including alkaline phosphatase (98.2% of cases), alanine aminotransferase (87.4% of cases), gamma-glutamyltransferase (85.7% of cases) and aspartate aminotransferase (62.2% of cases). Hyperbilirubinaemia is reported in 83.2% of the cases in the current literature (Center et al. 2009; Malek et al. 2013). Amylase and lipase are also elevated in some cases: 29.5% and 33.3% of reported cases, where measured on serum biochemistry, respectively (Malek et al. 2013; Worley et al. 2004). Cholesterol is often elevated (55.6% of reported cases where measured) (Worley et al. 2004). However, the most significant biomarkers associated with outcome were found to be elevated mean serum lactate concentration and decreased packed cell volume (Malek et al. 2013).

Ultrasoundography

The ultrasonographic appearance is diagnostic and well described in the literature. The classic GBM was described in earlier studies as a finely striated stellate pattern that differs from biliary sludge in that it is non-dependent (Besso et al. 2000). The most common abdominal ultrasonographic findings in dogs with clinically significant GBM include echogenic peritoneal fluid (more frequently confined to the gallbladder fossa), a thickened or laminated gallbladder wall, and an echogenic reaction in the gallbladder fossa (Crews et al. 2009). Ultrasoundographic signs of gallbladder rupture were 100% specific and included discontinuity.
of the gallbladder wall, hyperechogenicity of the cranial abdominal fat, free peritoneal fluid, or a free, well-organised mucocoele within the peritoneal cavity (Center 2009; Crews et al. 2009; Gaschen 2009) (Figures 1 & 2).

A study of 11 dogs that underwent cholecystectomy for GBM examined the relationship between the morphological appearance of the gallbladder content and the ultrasonographic pattern (Uno et al. 2009). This study described three ultrasonographic patterns, namely: pattern one, hyperechoic content filling the entire gallbladder or precipitated immobile content; pattern two, a thin hypoechoic exterior layer separated by an indistinct border from an internal hyperechoic area containing moth-eaten to mosaic-form hypoechoic areas; and pattern three, a thick hypoechoic area in the exterior layer separated by a distinctive border from a prominent internal hyperechoic area. This study concluded that pattern two was a forerunner of the typical kiwi fruit pattern diagnostic for GBM and should indicate the gallbladder dysmotility and cholangiohepatitis that often accompany this disease.

A more recent study examined the ultrasonographic findings and attempted to correlate these with clinical signs (Choi et al. 2014). A larger group of dogs (n = 43) was divided into six groups based on the ultrasonographic pattern, namely: type 1, immobile echogenic bile (23%); type 2, incomplete stellate pattern (30%); type 3, typical stellate pattern (12%); type 4, kiwi-like pattern and stellate combination (26%); type 5, kiwi-like pattern with residual central echogenic bile (9%); and type 6, kiwi-like pattern (0%). The ultrasonographic pattern was not associated with the clinical signs and is thus not a valid diagnostic tool for grading disease.

Gallbladder motility can also be evaluated ultrasonographically. Tsukagoshi et al. (2012) developed a gallbladder ejection fraction index that could be used to estimate dysmotility. Gallbladder volume was estimated on a longitudinal image post-12 hour starve and then 60 and 120 min postprandial (Hills a/d at 10 g per kilogram body weight) in order to calculate this index. This study proposes that gallbladder dysmotility is important in the aetiopathogenesis of GBM due to the increased exposure time of epithelial cells to bile salts.

**Scintigraphy**

Hepatobiliary scintigraphy is helpful in determining bile duct patency (Head & Daniel 2005). Findings in animals with chronic, complete EHB obstruction include reduced hepatic extraction fraction (which represents the portion of the radiopharmaceutical that is removed from the plasma on each circulatory pass through the liver), prolonged clearance half-life, inability to view the biliary tree and absence of radioactivity in the intestine (Head & Daniel 2005).

Hepatobiliary scintigraphy was performed in three dogs in the diagnostic work-up of GBM (Worley et al. 2004). Dogs were given 2–3 mCi of technetium Tc 99m-mebrofenin intravenously. All the scintigraphic scans revealed complete obstruction of the extrahepatic biliary system. This diagnostic technique requires registered facilities and has a considerable health and safety risk with accuracies that do not compete favourably with ultrasound.

**Bacteriology**

Approximately 13.5% of GBM have concurrent bacterial colonisation of the gallbladder (Amsellem et al. 2006; Malek et al. 2013; Mayhew et al. 2008; Pike et al. 2004; Uno et al. 2009; Worley et al. 2004). Ultrasound-guided cholecystocentesis is advised to collect a bile sample for bacterial culture and antibiogram testing in animals where medical management is pursued for cholecystitis. However, ultrasound-guided cholecystocentesis should be performed with caution if GBM is suspected as complication rates have not been determined (Center 2009). Complications associated with this procedure include bile leakage, bradycardia due to vagal stimulation, bacteraemia and local haemorrhage (Quinn & Cook 2009).
Histopathology
Cystic mucosal hyperplasia is often seen on microscopic examination of the affected gallbladder wall. Transmural ischaemic necrosis may be seen in the fundic region and precedes gallbladder rupture (Center 2009). The submission of all gallbladders post cholecystectomy is advised.

Treatment
Medical management
Large standardised prospective studies are still lacking for medical management of GBM and thus it cannot be recommended as the first line of treatment in dogs. It can be considered in asymptomatic animals and there are individual case reports supporting its use (Norwich 2011; Walter et al. 2008). However, all reported cases had concurrent hypothyroidism that needed to be addressed before resolution of GBM was possible.

Owners must be made aware that asymptomatic cases may develop into an acute clinical emergency should the disease progress to extrahepatic biliary obstruction or gallbladder rupture (Norwich 2011; Quinn & Cook 2009).

The foundation of medical management includes the use of choleretics and hepatoprotectants. Ursodeoxycholic acid is a naturally occurring hydrophilic bile acid that functions as a choleretic and hepatoprotectant at 10 mg/kg – 15 mg/kg PO, as a single dose or divided into two doses per day. S-adenosylmethionine is a naturally occurring precursor of cysteine that is essential in the production of the antioxidant glutathione, and therefore is hepatoprotectant at 18 mg/kg – 20 mg/kg PO, administered once daily on an empty stomach (tablets must not be split). A low-fat diet is encouraged, especially in animals with dyslipidaemias, as dietary management may stimulate biliary flow (Mitchell 2010; Norwich 2011). Concurrent endocrinopathies must be treated appropriately.

Regular monitoring of medically managed cases is recommended, with follow-up visits every 2–4 weeks for abdominal ultrasound, haematology and serum biochemistry. Any progression of the disease process warrants immediate surgical intervention (Center 2009; Quinn & Cook 2009).

Surgery
Surgical intervention for the treatment of GBM remains the therapeutic gold standard. Pre-operative haematology, serum biochemistry, urinalysis and coagulation profiles are recommended in all cases. Supplementing animals with vitamin K1 has been advocated pre-operatively, even in the light of normal coagulation profiles. This can be instituted by administering three doses of vitamin K1 at 0.5 mg/kg SC every 12 hours prior to surgery (Mitchell 2010; Quinn & Cook 2009). However, there are no published studies that support this recommendation.

Cholecystectomy is the recommended surgical procedure for the treatment of GBM. Microscopic examination of the gallbladder wall in cases of GBM indicates that it is diseased and this warrants its removal. However, it is crucial that the patency of the common bile duct is confirmed prior to cholecystectomy, either via manual normograde expression of the gallbladder or retrograde catheterisation of the common bile duct via duodenal enterotomy. The biliary tree must be flushed prior to ligation of the cystic duct in order to remove residual thick, inspissated bile and/or small choleliths to minimise the risk of post-operative biliary obstruction. The resected gallbladder is submitted for microscopic examination and bacterial culture. Liver biopsy (for histopathology, copper, iron and zinc concentrations) is indicated in all cases.

Laparoscopic cholecystectomy has been described for cases where biliary tract obstruction or rupture has been excluded (Mayhew et al. 2008). Cholecystotomy is not recommended as microscopic mural necrosis may be present and could result in post-operative gallbladder rupture. There are also documented cases of recurrence of GBM formation in dogs where cholecystotomy was initially performed (Center 2009).

Cholecystoenterostomy is feasible for rare GBM cases in which the patency of the common bile duct cannot be established. This procedure is, however, associated with a higher complication rate.

Recommended peri-operative care includes feeding a low-fat diet and broad-spectrum antimicrobial and hepatoprotectant therapy as described for medical management (Quinn & Cook 2009).

Prognosis and conclusion
The short- and long-term survival for biliary surgery is 66%, with the worst outcome in those dogs requiring cholecystoenterostomy (Amsellem et al. 2006). A peri-operative mortality rate of 21.7% – 40% is reported for dogs undergoing cholecystectomy for GBM. Most mortalities occur within the first 2 weeks after surgery, with long-term survival beyond this point being excellent. The most common complications include bile peritonitis, sepsis, disseminated intravascular coagulation and surgical-site dehiscence (Norwich 2011). Dogs diagnosed with concurrent pancreatitis are considered to have a poor prognosis (Amsellem et al. 2006). Elevation of the serum lactate concentration post-operatively and post-operative hypotension were significantly associated with a poorer clinical outcome (Malek et al. 2013). Conversely, published evidence indicates that the survival rate is not affected by bile leakage from gallbladder rupture nor from concurrent bacterial colonisation of the bile (Crews et al. 2009; Pike et al. 2004).

A small study examining 11 cases of GBM treated surgically and their corresponding ultrasonographic pattern found significant differences between the survivors and the non-survivors (Uno et al. 2009). The dogs that died were older
With GBM becoming an apparently increasingly common cause of extrahepatic biliary disease in canines, it is essential that clinicians become familiar with the current literature pertaining to this condition. However, further prospective studies with larger case numbers are necessary to clarify the intricacies of this disease.

Acknowledgements

Competing interests

The authors declare that they have no financial or personal relationships which may have influenced them in writing this article.

Authors’ contributions

T.M.S. (University of Pretoria) undertook the writing of this article and conducted the relevant literature review. L.S.K. (Ross University School of Veterinary Medicine) reviewed the literature and made significant contributions to the manuscript. A.K.C. (Vetinary Specialty Hospital of Hong Kong) reviewed the manuscript and contributed to the final review article.

References


http://dx.doi.org/10.1111/vru.12120
Author/s:
Smalle, TM; Cahalane, AK; Köster, LS

Title:
Gallbladder mucocoele: A review.

Date:
2015-12-09

Citation:

Persistent Link:
http://hdl.handle.net/11343/271255

License:
CC BY