CPD article

Gallbladder mucocele: a review, part 1

Gallbladder mucocele is defined as a build-up of immobile mucus within the gallbladder that can result in extrahepatic biliary obstruction, pressure necrosis of the gallbladder wall and ultimately, rupture. The incidence of this disease has increased steadily in veterinary medicine and now it is one of the most recognised extrahepatic biliary tract problems in the dog. This is not likely to solely be a result of an increased incidence of the disease, but more so the increasingly widespread use of ultrasonography to diagnose it. There are several proposed causes and predisposing factors of gallbladder mucocele, including mechanical or functional obstruction of the cystic duct, idiopathic dyslipidaemias, glucocorticoid excess and cholecystitis. Although clinicopathological changes are often present, they are not specific to the disease and the gold standard diagnostic imaging tool is ultrasonography.

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Gallbladder mucocele is defined as a build-up of immobile mucus within the gallbladder (*Figure 1*) that can result in extrahepatic biliary obstruction, pressure necrosis of the gallbladder wall and ultimately, rupture (Rogers et al, 2020). The rate at which dogs present with this disease has been steadily increasing and it is now one of the most commonly recognised extrahepatic biliary tract problems in the dog (Aguirre, 2017). Gallbladder mucoceles in cats are very rare and to the author's knowledge, have only been reported in the veterinary literature three times (Bennett et al, 2007; Moores and Gregory, 2007; Woods et al, 2012). This low incidence may be because of the lower number of mucus glands within the gall bladder wall of a cat compared to the dog (Center, 2009).

Anatomy and physiology of gallbladder

The gallbladder is a round organ situated between the quadrate and right medial liver lobes consisting of a fundus, body and neck (Evans and de Lahunta, 2013). The gallbladder connects to the duodenum via the cystic duct and the common bile duct and (Evans and de Lahunta, 2013). Five different layers are distinguished histologically in the gallbladder wall – the epithelium, mucosa, tunica muscularis externa, tunica serosa and tunica adventitia (Samuelson, 2006). When the gallbladder's main blood supply via the cystic artery is compromised, it becomes very vulnerable to ischaemic injury (Center, 2009), which may ultimately result in the rupture of the gallbladder wall. The gallbladder's principal role is to store bile, where it can be concentrated, acidified and modified before its release into the duodenum (Center, 2009). Although the gallbladder and bile have a role in the digestive process, it is not an essential organ and cholecystectomy is well tolerated (Center, 2009).

Aetiopathogenesis

The aetiology and pathogenesis of gallbladder mucocele is still not fully understood and is thought to be a consequence of multiple factors, both genetic and environmental (Crews et al, 2009).

One proposed cause of gallbladder mucocele is mechanical (for example, cholelith) or functional obstruction of the cystic duct (for example, decreased wall peristalsis) (Besso et al, 2000). Decreased outflow of bile from the gallbladder will increase

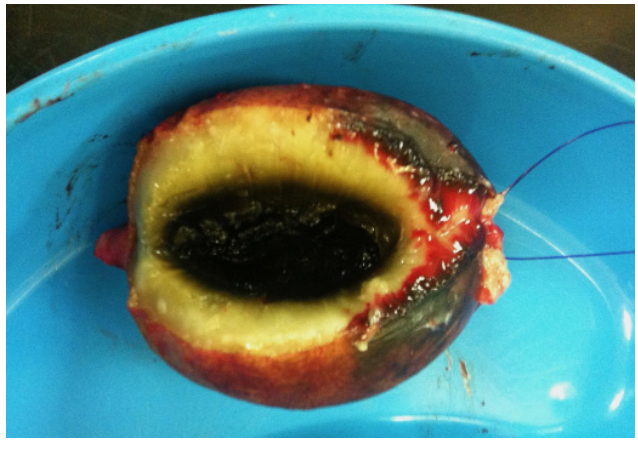

Figure 1. Gallbladder mucocele removed from a dog.

mucin production by the mucosal glands inside the gallbladder wall (Besso et al, 2000). Although in a healthy animal, mucin has an important role in protecting the gallbladder wall from concentrated bile constituents, it can also cause the development of gallbladder disease by decreasing normal bile flow (Jüngst, 2001). Chronic progressive biliary sludging has been proposed to result in the formation of mucocele (Besso et al, 2000), although another study conducted over a 12-month period did not confirm this to be a cause on its own (DeMonaco et al, 2016).

Idiopathic dyslipidaemias in some breeds, such as Shetland Sheepdogs and Cocker Spaniels (American and English), have been named as predisposing factors in the development of the problem (Aguirre et al, 2007). Cocker Spaniels on different continents have different genotypes and thus have different predispositions to gallbladder mucocele and other hepatobiliary diseases (Allerton et al, 2018). For example, American Cocker Spaniels in Japan have been shown to develop chronic hepatitis that is phenotypically different to cases diagnosed in North America and Europe (Kanemoto et al, 2013). It is likely that this difference in genetic predisposition to gallbladder mucocele is also true for other breeds on different continents.

Other predisposing factors include glucocorticoid excess, cholecystitis, treatments using progesterone and hypothyroidism (Aguirre et al, 2007). These conditions can alter bile and mucin composition (Kook et al, 2012) or gallbladder wall motility (Tsukagoshi et al, 2012).

A study by Allerton et al (2018) showed a higher breed disposition in Border Terriers in the UK compared to other breeds. Unfortunately the cause for this was not determined, but it was demonstrated by the researchers that endocrinopathies were not associated with the development of gallbladder mucocele in that breed.

Aguirre (2017) proposed that the main cause of gallbladder mucocele in cats might be biliary stasis, as the endocrinopathies that have been attributed to mucocele formation in dogs occur infrequently in cats. This study discussed that about 12% of cats have congenital biliary abnormalities and proposed that this might precede biliary diseases in felines.

Diagnosis

Although clinical signs and clinicopathological findings are not specific to gallbladder mucocele, diagnosing it is relatively easy because of its specific ultrasonographic features.

Signalment

Choi et al (2014) reported that the mean age of dogs diagnosed with gallbladder mucoceles was 9.32 years old (range from 4–15 years). In this study, there were more female than male dogs enrolled (24 versus 19 respectively) and only 56% of the dogs showed any clinical signs. Similar age and sex distribution was also seen in a study by Allerton et al (2018); most dogs in the gallbladder group were middle to old aged (median age 9 years 11 months, ranging from 5–14 years) and almost half were neutered females. In a study by Besso et al (2000), smaller breeds were more affected (64% of the affected dogs weighed less than 20 kg). There seems to be an evident breed predisposition in which Shetland Sheepdogs (Aguirre et al, 2007), Cocker Spaniels, Miniature Schnauzers, Border Terriers and Pomeranians are overrepresented (Besso et al, 2000; Norwich, 2011; Malek et al, 2013; Allerton et al, 2018). Other breeds in which the problem has been reported more frequently include Chihuahuas, Miniature Dachshunds, Yorkshire Terriers and Shiba Inus (Kutsunai et al, 2014).

Concurrent diseases

In a study by Kutsunai et al (2014) it was shown that dogs with mucoceles often have a concurrent disease that may contribute to the mucocele formation. The researchers found that dogs with mucoceles often have concurrent pancreatitis. Other implicated diseases included hepatitis, protein losing enteropathy, renal failure, vacuolar hepatopathy, hypothyroidism, hyperadrenocorticism and lymphoma. Altogether, 38/58 dogs in the gallbladder mucocele group had a concurrent disease (Kutsunai et al, 2014).

Clinical signs

Clinical presentation can vary as a result of the slow onset of this disease (Aguirre, 2017). According to a study by Jaffey et al (2019) that included 1194 dogs with gallbladder mucoceles, about 82% of dogs had at least one clinical sign. The most commonly seen clinical signs in this study were vomiting, lethargy and anorexia. Less commonly reported signs included diarrhoea, painful abdomen, hyporexia and jaundice. According to a study by Besso et al (2000) that looked at 14 dogs with gallbladder mucoceles, hyperthermia occurs in dogs with bacterial cholecystitis, acute rupture, or loss of gall bladder wall integrity.

Clinicopathological findings

The most common clinicopathological findings, as reported in a study by Worley et al (2004), are high serum activities of alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and γ-glutamyltransferase, as well as high serum or plasma total bilirubin, cholesterol, globulin, blood urea nitrogen and creatinine concentrations. The same researchers found that serum thyroxine and albumin concentrations were below normal reference interval levels. Hyperlipidaemia is a more common finding than hypercholesterolaemia, but both can be within normal limits in less than one third of dogs (Jaffey et al, 2019).

The most common haematological abnormality reported in gallbladder mucocele patients is neutrophilia. Of these neutrophilic patients, 21% demonstrate a 'left shift' (Worley et al, 2004). Anaemia is a frequent finding, present in 36% of patients. Other significant findings may include lymphopenia, monocytosis and low haemoglobin concentration (Worley et al, 2004). Preoperative hyperlactatemia and anaemia have been associated with poor prognosis (Malek et al, 2013).

Not much is known about the pathophysiology of coagulation disorders in dogs with gallbladder mucocele, but a study by Pavlick et al (2021) showed that most dogs are in a hypercoagulable state based on thromboelastographic findings. Other clinicopathological markers measured (complete blood count, activated partial thromboplastin time, factor VIII, protein C, von Willebrand's factor, antithrombin activity, fibrinogen, and D-dimers) showed that a mixed coagulation disorder

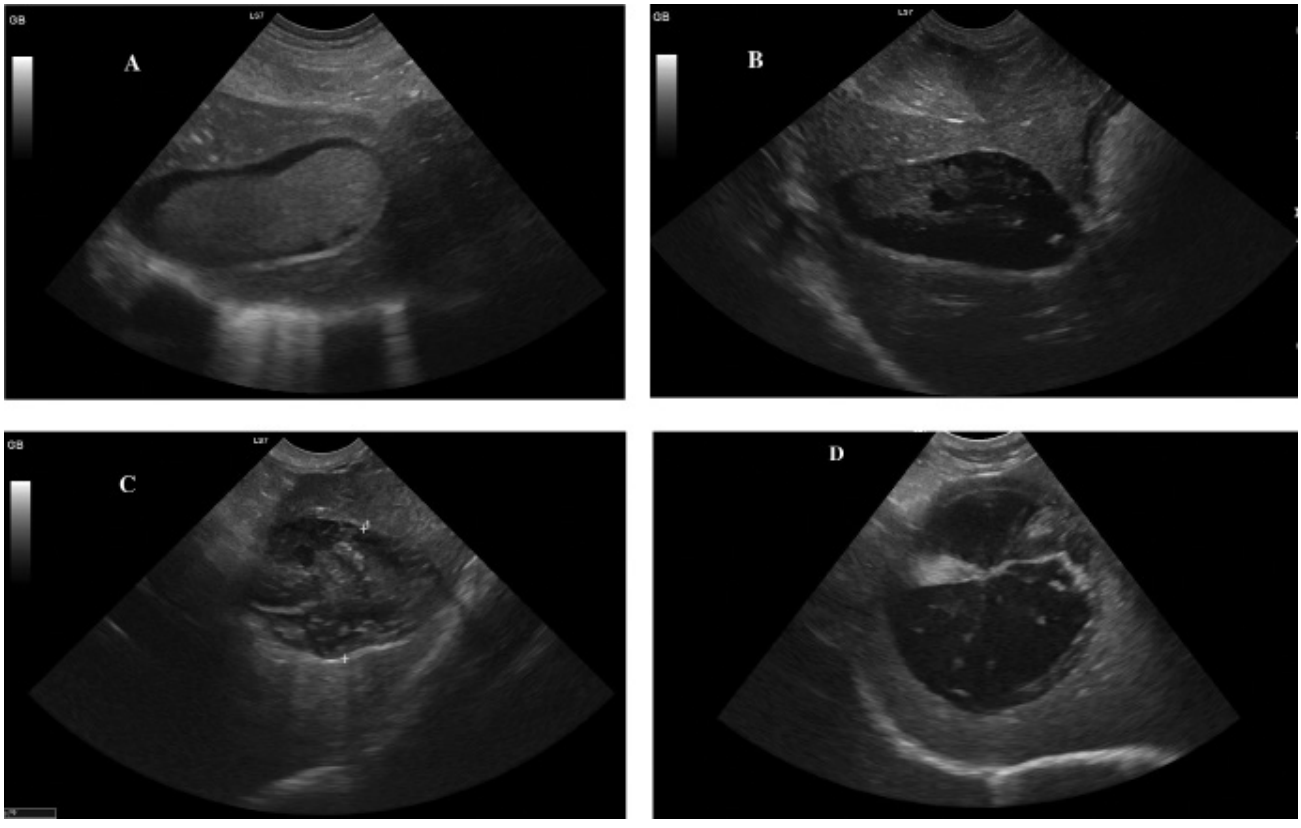

Figure 2. a) Marked amount of echogenic bile positioned centrally in the gall bladder surrounded by thin hypoechoic rim. b) Moderate amount of mildly organised echogenic bile centrally positioned in the gall bladder surrounded by thick hypoechoic rim. c) Mildly heterogenous well organised echogenic bile that occupies the entire gallbladder lumen. d) Echogenic bile organised into a typical stellate pattern characterised by radiating hyperechoic striations alternated by anechoic bile.

Table 1 . Classification of gallbladder mucoceles

Gallbladder mucocele type	Ultrasonographic findings
1	Immobile echogenic bile
2	Incomplete stellate pattern
3	Typical stellate pattern
4	Kiwi-like pattern and stellate combination
5	Kiwi-like pattern and residual central echogenic bile
6	Kiwi-like pattern
Rupture	Incomplete gall bladder wall with hyperechoic bile in cranial abdomen

Adapted from Parkanzy et al (2019)

is likely present. In another large multicentric study, 8% of cholecystectomised dogs died from documented thromboembolic events (for example, pulmonary thromboembolism and splenic vein thrombosis) (Jaffey et al, 2019).

Urinalysis

A study by Lindaberry et al (2021) showed that dogs with gallbladder mucoceles had increased protein levels in their urine. Urine protein creatinine ratio was not measured in all dogs, but was found to be 0.82–6.7 in dogs with gallbladder mucoceles and 0.1–0.14 in dogs in the control group. This finding likely contributes to the hypercoagulable state found in dogs with gallbladder mucoceles.

Diagnostic imaging

The gold standard diagnostic imaging tool for gallbladder mucocele is ultrasound (Pike et al, 2004). In almost all cases, the gallbladder is found to be large when measured (Besso et al, 2000). Gallbladder volume can be determined using the ellipse formula (volume=π/6×L×H×W; L – length, H – dorsoventral diameter, W – right-to-left width) (Besso et al, 2000). The gallbladder is full or mostly filled with non-gravity-dependent echogenic sediment that can be either finely striated and/or stellate (Besso et al, 2000) (*Figure 2*). In more than half of cases, the cystic duct and common bile duct are distended (Besso et al, 2000) (Crews et al, 2009). Finding echogenic peritoneal fluid or echoic material in the cranial abdomen is also very common (Crews et al, 2009). The latter is related to gallbladder wall rupture, which can be confirmed on ultrasound if wall continuity is not detected (Pike et al, 2004). Cranial abdominal fat is more hyperechoic if there is free fluid present in the abdomen (Pike et al, 2004).

Gallbladder mucoceles can be divided into groups based on ultrasonographic findings. Classification of gallbladder mucocele is found in *Table 1* (Parakanzky et al, 2019).

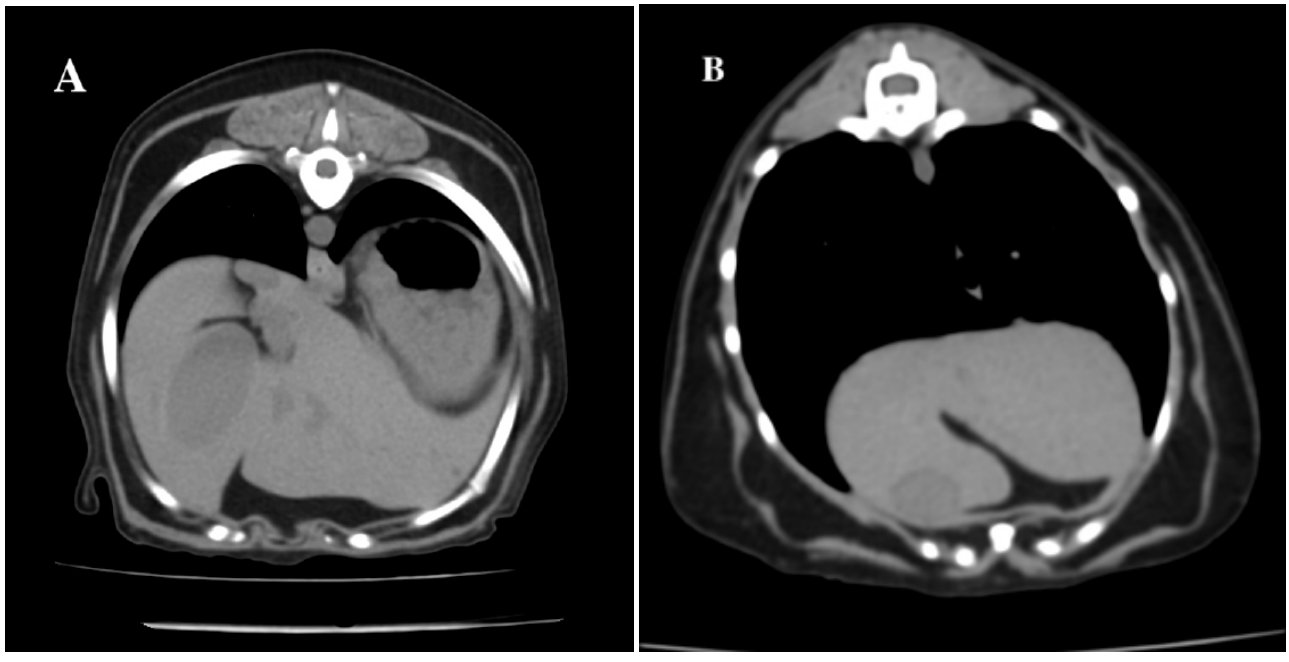

Figure 3. a) Normal gallbladder. b) Hyperattenuating bile with a lucent halo surrounding it.

Different gallbladder pathologies can have similar findings on a computed tomography (CT) scan. The most common findings on a CT scan of dogs with mucoceles are mineral or hyperattenuating material within the gallbladder, gallbladder wall thickening, nodules or masses in the gallbladder and abdominal effusion (*Figure 3*) (Brand et al, 2020).

Microbiology and histological findings

Histological samples that are collected during cholecystectomy reveal necrosis, infarction, serosal fibrosis, lymphocytic plasmocytic cholecystitis and suppurative cholecystitis (Malek et al, 2013). The incidence of cholecystitis in dogs with concurrent gallbladder mucocele varies widely across different studies. It has been published that 4–68% of dogs with gallbladder mucoceles have concurrent signs of cholecystitis on histopathological evaluation (Rogers et al, 2020; Wennogle et al, 2019).

Positive bacterial culture has been obtained from 8–66% of dogs in various studies (Crews et al, 2009; Besso et al, 2000; Pike et al, 2004). This difference in results might be a result of antibacterial therapies that have been started during different stages of the disease and treatment. The most commonly isolated species are *Escherichia coli*, *Streptococcus* spp., *Enterococcus* spp., *Pseudomonas aeruginosa*, *Bacillus* spp., gram-negative bacilli and gram-positive cocci (Crews et al, 2009). No strong association has been established between bacterial cholecystitis, positive bacterial culture and survival (Rogers et al, 2020).

Conflicts of interest

The author declares that there are no conflicts of interest.

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KEY POINTS

- Gallbladder mucocele is a build-up of immobile mucus within the gallbladder.
- The main causes and predisposing factors are mechanical or functional obstruction of the cystic duct, idiopathic dyslipidaemias, glucocorticoid excess, and cholecystitis.
- The gold standard diagnostic imaging tool is ultrasonography.

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