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Diagnosis and management of gallbladder mucocele formation in dogs

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Abstract
The past 20 years have observed the emergence of an enigmatic and deadly disease in dogs referred to as *gallbladder mucocele formation*. The disease has been the subject of over 100 PubMed-indexed publications, yet only a single review of the topic has been published approximately 10 years ago. The aim of the current review was to provide a practical overview of the current literature of and, in some cases, the authors' experience in the diagnosis and management of gallbladder mucocele formation in dogs. Key takeaways were that gallbladder mucocele formation is caused by secretion of abnormal mucus by the gallbladder epithelium and has a predilection for older, small-sized purebred dogs. These dogs are often concurrently diagnosed with hypothyroidism, hyperadrenocorticism, hyperlipidemia, and proteinuria. Diagnosis is reliant on ultrasonographic features demonstrating the presence of non–gravity-dependent mucus that is adherent to the walls of the gallbladder and encroaching into the lumen. The definitive treatment for mucocele formation is cholecystectomy, which carries a significant short-term mortality but good long-term prognosis.

Keywords: cholecystectomy, mucocele, gallbladder rupture, abdominal ultrasound, surgical complications

Gallbladder mucocele formation in dogs is characterized by secretion of abnormally thick, immobile, and rubbery mucus by the gallbladder epithelium.[1] The condition was rarely reported prior to 20 years ago[2,3] and has emerged as one of the most common, deadly, and poorly understood causes of gallbladder disease in the dog.[4–16] However, only a single review[17] of the specific topic has been published. Gallbladder mucocele formation can be discovered as an incidental finding during abdominal ultrasound examination that is performed for another indication or diagnosed in dogs that present with systemic illness secondary to the consequences of accumulated mucus within the gallbladder. Gallbladder mucocele formation afflicts older dogs (median age, 10 years) and has a strong predilection for small-sized purebred dogs including Shetland Sheepdogs, Border Terriers, Cocker Spaniels, Pomeranians, Miniature Schnauzers, Chihuahuas, Pugs, Bichon Frises, and Beagles, as well as others.[6,18] Gallbladder mucocele formation is less common in mixed-breed dogs (approx 10% of cases).[13] There does not appear to be a sex predilection.

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Pathogenesis

In dogs that form a mucocele, the gallbladder epithelium secretes copious amounts of gel-forming mucus.[1] Rather than dispersing over the surface of the epithelium, the mucus remains dehydrated and tethered to the epithelium, where it accumulates in concentric layers over time until the gallbladder lumen is filled with solidified mucus **(Figure 1)**.

The underlying defect that appears to cause abnormal mucus behavior in dogs with mucocele formation is failure of the gallbladder epithelium to hydrate the mucus. This is caused by abnormal function of an epithelial chloride channel called the *cystic fibrosis transmembrane conductance regulatory* (CFTR) *channel*.[19] Genetic defects in the CFTR channel are responsible for the disease called *cystic fibrosis* in people. Dogs with mucocele formation do not appear to have a genetic defect in CFTR but rather an acquired form of dysfunction of the channel.[19] The reason for this abnormality is currently unknown. More poorly understood aspects of gallbladder mucocele formation in dogs include a high prevalence of hypothyroidism, hyperadrenocorticism, hyperlipidemia, and proteinuria, suggesting that the disease involves more than just the disruption of gallbladder function.[16,20–23]

Mucocele formation may progress slowly and never culminate in clinical signs in some dogs. In other dogs, progression of mucocele formation can lead to major adverse outcomes including arterial infarction

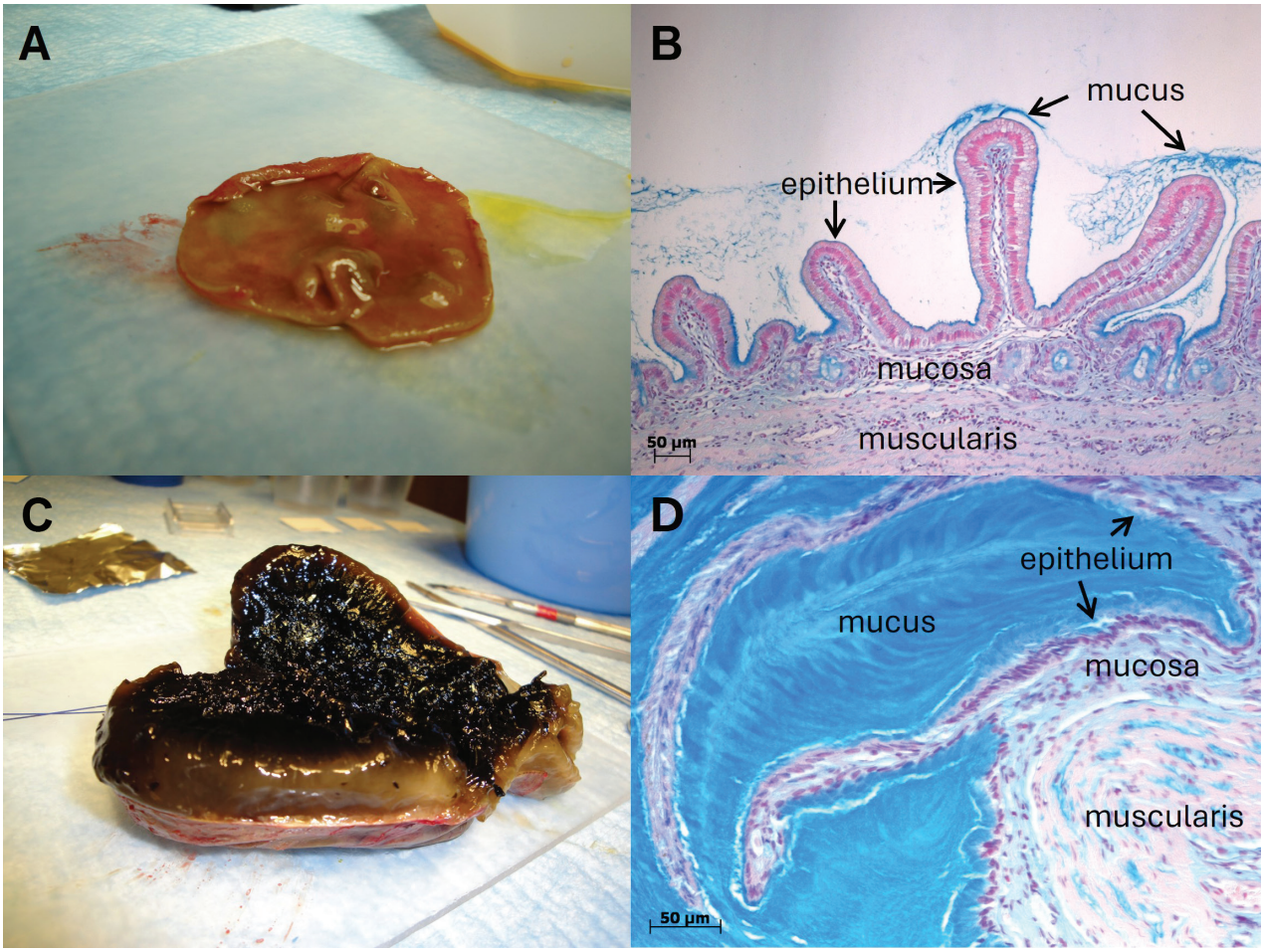

Figure 1—Gross and microscopic appearance of normal and mucocele canine gallbladders. Appearance of a transected gallbladder from a normal dog (A) and dog with mucocele formation (C) is shown. The normal canine gallbladder contains a watery mucus that protects the mucosa. Mucocele gallbladders contain solidified mucus that arises from and remains attached to the mucosal epithelium. Histologic appearance of normal (B) and mucocele (D) canine gallbladder mucosa is shown. Sections are stained with Alcian blue, which stains mucus blue. Normal gallbladders are lined by simple columnar epithelium that hydrates and disperses the mucus, resulting in infrequent visualization of mucus in histologic sections. In canine mucoceles, mucus remains tethered to the epithelium where it accumulates over time in concentrically lamellar layers with distinct ribbons of mucus extending perpendicularly in columns from each epithelial cell and eventually leading to obliteration of the gallbladder lumen. Surrounded by mucus, the mucosal folds become slender and trabeculate and frequently create cystic spaces in which mucus can reside. (Reproduced from Kesimer M, Cullen J, Cao R, et al. Excess secretion of gel-forming mucins and associated innate defense proteins with defective mucin un-packaging underpin gallbladder mucocele formation in dogs. *PLoS One*. 2015;10[9]:e0138988. doi:10.1371/journal.pone.0138988. Reprinted under terms of the Creative Commons Attribution license.)

of the gallbladder wall, secondary bacterial infection of the gallbladder, biliary outflow obstruction by gallbladder mucus, or rupture of the gallbladder under the pressure of the accumulated mucus **(Figure 2)**.

Diagnosis

Clinical signs

In some dogs, mucocele formation is an incidental finding when abdominal ultrasound is performed for a different indication (eg, tumor staging, examination of adrenals in dogs with hyperadrenocorticism). When present, clinical signs attributed to gallbladder mucocele formation can range from nonspecific gastrointestinal distress to progressive cholestasis or acute peritonitis. The more common clinical signs and physical examination abnormalities in dogs with symptomatic gallbladder mucocele formation include vomiting, anorexia/inappetence, lethargy, abdominal pain, icterus, and fever.[13] These signs are presumably secondary to gallbladder pain, gallbladder rupture, gallbladder infarction, gallbladder infection, or common bile duct obstruction. Clinical signs are often acute and frequently vague enough to be attributed to more common differential diagnoses such as pancreatitis or acute gastroenteritis.

Clinical pathology abnormalities

Clinical pathology abnormalities can increase suspicion for mucocele formation but are not diagnostic and cannot differentiate between dogs that have developed gallbladder rupture, common bile

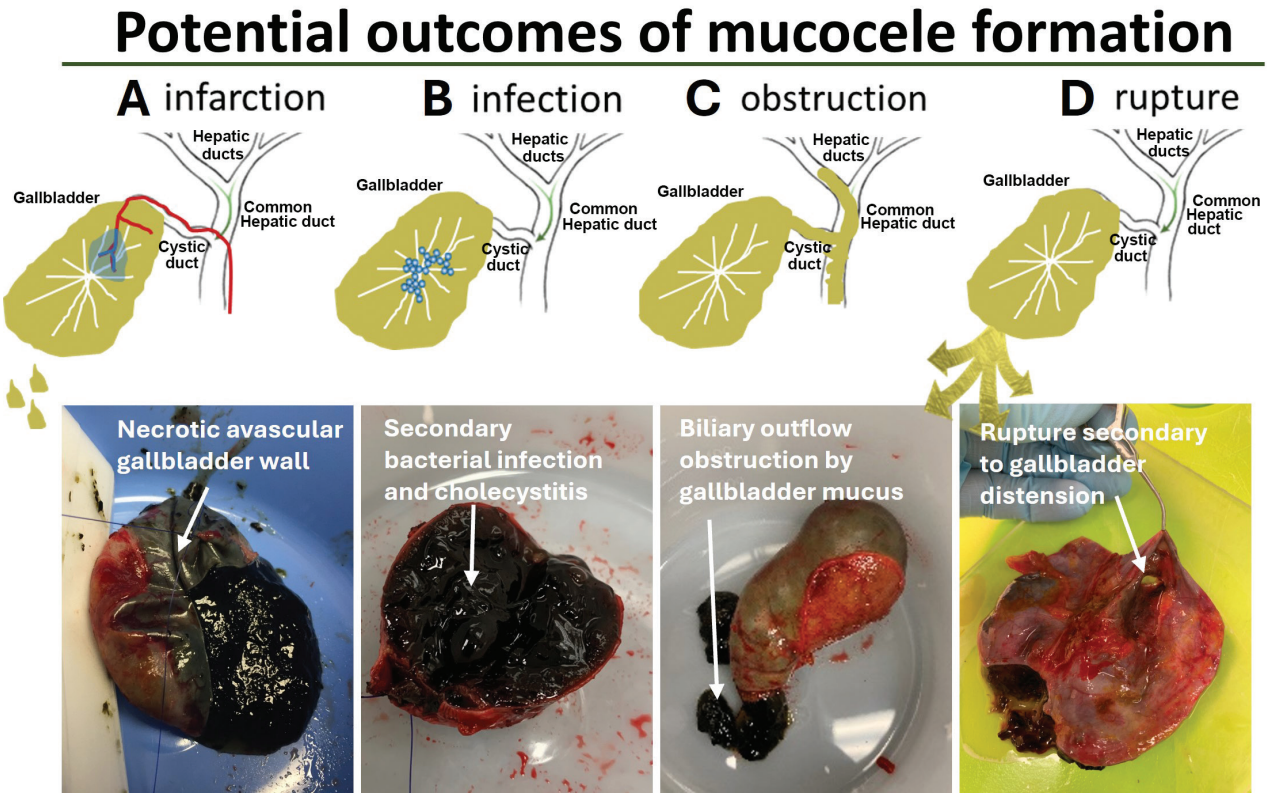

Figure 2—Four clinical outcomes of mucocele formation. A—Gallbladder wall infarction and necrosis. B—Secondary bacterial infection leading to superimposed cholecystitis. C—Extrahepatic bile duct obstruction by mucus plugs. D—Progressive accumulation of mucus leading to rupture under pressure.

duct obstruction, gallbladder infarction, or gallbladder infection. The most common CBC and serum biochemistry profile abnormalities in dogs with mucocele formation include an inflammatory leukogram and elevations in ALP, ALT, GGT, triglycerides, and cholesterol. Approximately half of symptomatic dogs will have an elevated serum total bilirubin at the time of diagnosis of gallbladder mucocele formation.[4–6,21,24] The most common causes for elevated total bilirubin in dogs with gallbladder mucocele formation include gallbladder rupture with bile peritonitis, extrahepatic biliary tract obstruction by mucus, bacterial infection of the gallbladder mucocele, concurrent pancreatitis, or coexisting primary hepatic disease. Importantly, many dogs with gallbladder rupture will have a normal serum bilirubin. This is because rupture of the gallbladder mucocele oftentimes only extrudes mucus, rather than liquid bile, into the abdomen.[25]

Abdominal ultrasound imaging

Abdominal ultrasound is the key to diagnosis of mucocele formation. Disease awareness and growing use of abdominal ultrasonography have contributed to increasing diagnosis and *misdiagnosis* of gallbladder mucocele formation in dogs. The classic ultrasonographic appearance of mucocele formation is the finding of an enlarged gallbladder containing immobile/non–gravity-dependent content with a finely striated or stellate pattern reminiscent of a slice of kiwifruit. However, the appearance of a mucocele can show considerable variation.

In general, the ultrasonographic appearance of gallbladder mucocele mucus will be anechoic (black), extend from a fixed position on the gallbladder walls into the lumen, and accumulate over time until the gallbladder is filled with mucus. More central gallbladder contents can consist of liquid, gelatinous sludge, or crumbly-dry material; appear hyperechoic, hypoechoic, or a mixture of both; and become smaller in volume over time. These changes in appearance as the gallbladder progresses from early and immature to mature mucocele formation create what are referred to as *bile patterns* or *mucocele types* **(Figure 3)**.[9,10,12,26]

The key to establishing how much of the gallbladder content remains mobile is to observe the gallbladder contents for fluid motion or gravity dependence. This is best accomplished during the ultrasound examination by reexamining the gallbladder after the patient has been maintained in lateral recumbency for approximately 10 minutes and assessing whether the thicker sludge has moved to a gravity-dependent location (ie, "settled out") in the gallbladder. Mobile sludge will often form a fluid level between the more liquid and thicker portions **(Figure 4)**.

While the patterns are helpful to diagnose mucocele formation and ascertain how mature the mucocele is likely to be, clinical signs do not predictably

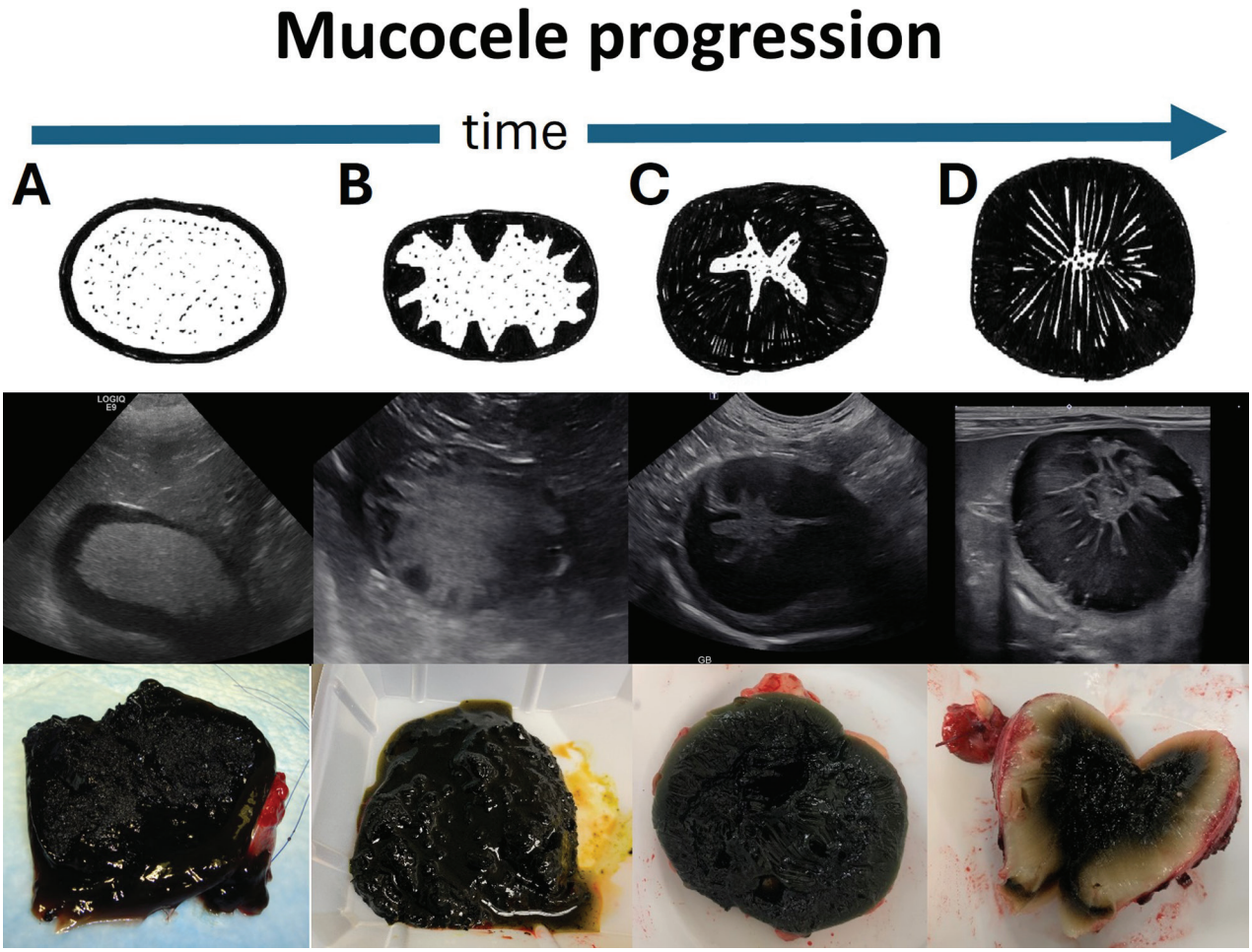

Figure 3—Simplified schematic of ultrasonographic progression of mucocele formation. A—Early mucocele formation: hypoechoic (black) rim of mucus attached to the gallbladder wall with central echogenic mobile or immobile sludge. B—Immature mucocele: ridges of hypoechoic mucus extending from and attached to the gallbladder wall with central echogenic mobile or immobile sludge. C—Mature mucocele: hypoechoic mucus attached to the gallbladder wall and nearly obliterating the gallbladder lumen with a small volume of central echogenic mobile or immobile sludge. D—Hypermature mucocele: highly compressed hypoechoic mucus obliterating the gallbladder lumen with fine hyperechoic striations radiating centrally.

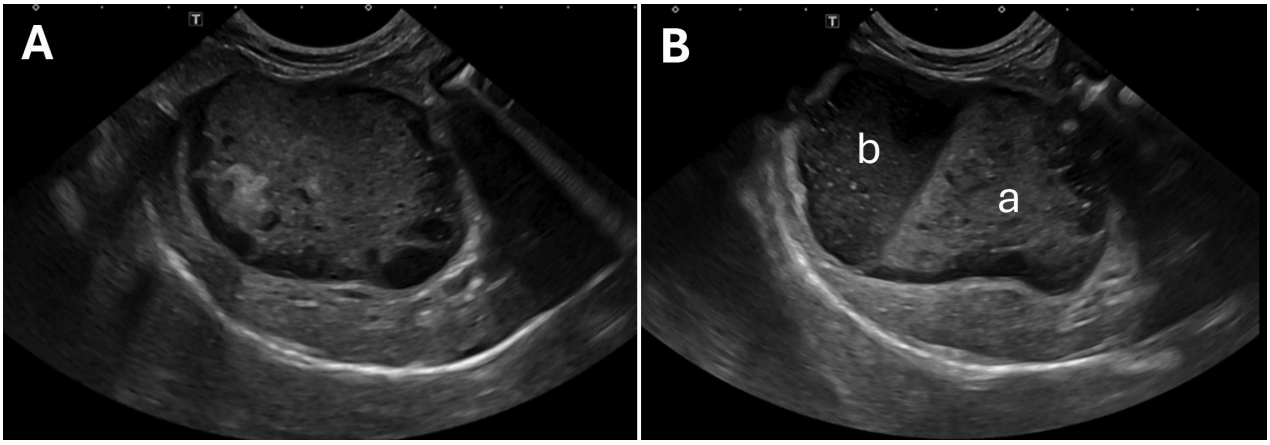

Figure 4—Suspended gallbladder sludge may be mistaken for a mucocele. A—Presumptive immature mucocele with peripheral ridges of hypoechoic mucus and central hyperechoic sludge. Suspended sludge can be interpreted as inspissated material unless close attention is paid to fluid motion as well as gravity-dependent settling of gallbladder sludge. B—The same gallbladder after the patient remained in lateral recumbency for 10 minutes. The thicker, more echogenic sludge has now settled in the gravity-dependent portion of the gallbladder (a), forming a fluid level with the more liquid, hypoechoic bile (b), confirming mobility of the gallbladder contents.

correlate with maturity of the mucocele.[26] In other words, dogs can be clinically ill due to gallbladder infarction, gallbladder infection, or bile duct obstruction even at early stages of mucocele formation. Note that fine-needle aspiration of the gallbladder to obtain a sample for bacterial culture is contraindicated due to risk of gallbladder rupture and solidified contents that are not easily aspirated.

Detection of gallbladder rupture

Several studies[9,11,24,26,27] confirm that ultrasound is not sensitive for the detection of gallbladder rupture (sensitivity range, 56% to 93%). Important ultrasonographic warning signs of impending or overt loss of gallbladder wall integrity in dogs with mucocele formation include evidence of hyperechoic mesentery or fluid in the region of the gallbladder, abdominal effusion, disruption of the gallbladder wall, dilated common bile duct, mucoid debris in the common bile duct, or overt clumps of gallbladder mucus in the abdomen **(Figure 5)**.[5,28,29] Extruded gallbladder mucoceles can retain their characteristic striated appearance and move considerably from the gallbladder fossa.[25,26]

If sufficient volume is present, abdominal effusion should always be sampled. Be aware that abdominal effusion bilirubin concentration cannot be used to rule out bile peritonitis in dogs with suspected rupture of a gallbladder mucocele. This is because many dogs simply rupture mucus, rather than liquid bile, into their abdominal cavity. Abdominal fluid should always be examined cytologically, as mucocele mucus may appear in the effusion as long, dense, fibrillary strands of bright blue to blue-gray material.[30] This finding, if found, is pathognomonic for mucocele rupture.

There are no distinguishing differences between the type of clinical signs observed or presence of hyperbilirubinemia in dogs with and without rupture.[27] While dogs with rupture may have higher serum ALP, ALT, lactate, and WBC, these findings have limited value in determining rupture on a case-by-case basis.[5,7]

Recent descriptions of contrast-enhanced ultrasonography hold promise in improving the sensitivity (100%) and specificity (100%) of ultrasound for the diagnosis of gallbladder necrosis or rupture in dogs, but its use is limited by unavailability and expense of the contrast agent.[31] More recently, increases in serum C-reactive protein concentration was described to be comparable in sensitivity to routine abdominal ultrasound for supporting a diagnosis of gallbladder rupture in dogs.[27] However, increased C-reactive protein in serum of dogs without rupture due to concurrent inflammatory conditions (eg, pancreatitis) limits the specificity of this measurement.

Surgical Management

Cholecystectomy is currently the recommended treatment for dogs with asymptomatic and symptomatic gallbladder mucocele formation. When surgery is performed electively on dogs with incidental/asymptomatic mucocele formation, the average mortality is approximately 5%. Elective surgery is associated with fewer intraoperative complications, and postoperative complications are more often minor. In contrast, dogs that have developed symptomatic disease and require nonelective surgery have an average mortality of 17% to 23%.[13,32–34] In symptomatic dogs, approximately 25% will have evidence of rupture or previous bile leakage observed at the time of surgery. Detection of rupture is associated with 2.7 times the risk of mortality. Presurgical factors associated with increased mortality in dogs undergoing cholecystectomy, in addition to the presence of symptomatic disease, include older age, jaundice/hyperbilirubinemia, magnitude of increase in ALP and ALT, azotemia, hyperlactatemia, advanced maturity of the mucocele, and concurrent diagnosis of hyperadrenocorticism.[11,13,24,33–35] Surgical mortality is greatest in the immediate postoperative period.[13] Pulmonary complications predominate as a cause of death in these patients and include acute pulmonary thromboembolism, acute lung injury, aspiration pneumonia, hypoxemia, and respiratory arrest. Other causes of death or euthanasia in these dogs include surgery-related complications (bile peritonitis, biliary obstruction, sepsis), acute organ injuries such as acute kidney injury, pancreatitis, peritonitis, and multiorgan system dysfunction. Due to the significant intraoperative challenges and intensive postoperative care required for these patients, referral to a surgical specialist with access to intensive postoperative care is essential.

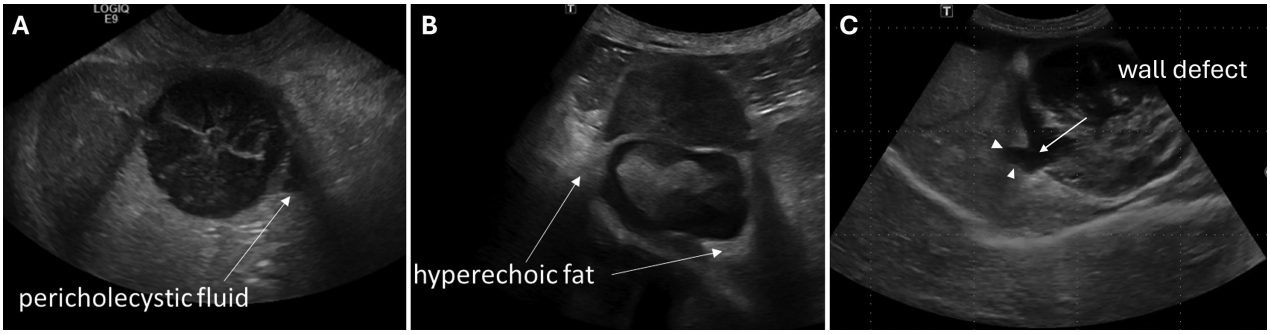

Figure 5—Ultrasonographic signs of gallbladder rupture. A—A small amount of hypoechoic fluid has accumulated adjacent to the gallbladder (arrow). B—The pericholecystic fat is markedly hyperechoic (arrows). C—A focal defect is visible in the gallbladder wall (arrow), with a small amount of fluid accumulation next to the gallbladder (arrowheads). The fat surrounding the gallbladder is hyperechoic.

Biliary Infection

Positive results of aerobic and/or anaerobic culture of gallbladder contents in dogs with mucocele formation range from 15% to 20%.[11,12,34,36] Reported bacteria are generally typical of those observed in cases of bacterial cholangitis/cholecystitis and include gram-positive aerobes (eg, *Enterococcus* spp, *Streptococcus* spp, Staphylococcus spp), gram-negative aerobes (*Escherichia coli*, *Pseudomonas* spp), and anaerobes (*Clostridium* spp, *Bacteroides* spp, *Bacillus* spp). Consequently, empirical treatment pending culture results is necessarily broad spectrum. Duration of treatment of documented infection is unestablished but generally 2 to 4 weeks. In some studies,[11,33] there is no reported association between survival and positive bacterial culture results or history of antibiotic administration, while another study[34] reports increased mortality in dogs with positive culture results. Establishing these outcomes is difficult due to different sample types cultured, different culture methods, pre- versus intraoperative antibiotic exposures, and choice/duration of antibiotics. In the absence of culture results, whether dogs should be empirically treated with antibiotics is unclear.

Persistent or Recurrent Liver Enzyme Elevations After Cholecystectomy

There is little published regarding postsurgical resolution of abnormal liver enzyme activities, hyperlipidemia, or proteinuria in dogs with mucocele formation. Most dogs have significant improvement in abnormal clinicopathological findings; however, persistent increases above normal may be observed in up to 75% of dogs.[7] As a starting point, differential diagnoses that should be considered in dogs with persistent or recurrent increases in liver enzyme activities after cholecystectomy include biliary bacterial infection (preexisting or newly acquired), partial extrahepatic biliary obstruction with mucus debris or small choleliths, pancreatitis, undiagnosed or unregulated hyperadrenocorticism, and concurrent primary hepatic disease. Collection of a liver biopsy at the time of cholecystectomy enables the determination of whether there is concurrent hepatic disease that can be addressed. Additional diagnostics to consider in patients with persistent or recurrent liver enzyme elevations include abdominal ultrasound to examine the liver, pancreas, and common bile duct; fine-needle aspirate of the liver for bacterial culture or treating with an empirical course of antibiotics; and testing for hyperadrenocorticism and hyperlipidemia.

Histopathology Findings

Gallbladder

On histologic examination, the gallbladder mucosa is characterized by long, thin, and branching fronds of well-differentiated gallbladder epithelial cells whose apical cytoplasm is filled with mucus granules. Secreted mucus appears attached to the epithelial cells and extends as a solid sheet into the lumen (Figure 1). Inflammatory infiltrates are generally uncommon except in cases of bacterial infection, gallbladder necrosis/rupture, or gallbladder arterial thrombosis (infarction).

Liver

Dogs undergoing surgery for cholecystectomy should also have liver biopsy specimens obtained for histopathologic examination. Common findings include moderate to severe vacuolar hepatopathy (possibly associated with concurrent endocrinopathy), mild to moderate periportal neutrophilic or mixed inflammatory infiltrates, and evidence of extrahepatic obstruction characterized by bile duct proliferation and portal fibrosis.[4,6–8,37] Although uncommon, liver biopsy can sometimes disclose a significant underlying primary liver disease or evidence of hepatobiliary bacterial infection that warrants intervention. Accordingly, the decision to invest in liver biopsies at the time of surgery can be priceless, especially for dogs with persistent postoperative liver enzyme activities.

Diagnosis and Management of Concurrent Illness in All Dogs With Mucocele Formation

Endocrinopathy

Dogs with mucocele formation have greater odds of being diagnosed with hyperadrenocorticism and/or hypothyroidism than dogs without mucocele formation.[16,20] The prevalence of hyperadrenocorticism among dogs with mucocele formation ranges from 6% to 23% and hypothyroidism from 5% to 14%. The presence of hyperadrenocorticism is associated with increased odds of death in dogs undergoing cholecystectomy for mucocele formation.[13] Because these endocrinopathies might play a role in promoting mucocele pathogenesis, concurrent hyperadrenocorticism or hypothyroidism should be considered in all dogs diagnosed with mucocele formation.

At a minimum, all dogs should have ultrasound of the adrenal glands performed at the time of diagnosis of mucocele formation. Due to the confounding influence of concurrent illness, diagnostic testing for hypothyroidism should be based on results of a comprehensive thyroid profile. Thyroid testing should be performed at the time of diagnosis if mucocele formation is incidental, when clinical signs are least severe, or following recovery from surgery if performed emergently. Diagnostic testing for hyperadrenocorticism should be based on clinical suspicion with similar considerations for timing. In all dogs with mucocele formation, care should be taken to minimize exogenous steroid administration.

Hyperlipidemia

Dogs with mucocele formation have greater odds of being diagnosed with hypercholesterolemia and/or hypertriglyceridemia than dogs without mucocele formation.[21] Several breeds of dogs that are predisposed to mucocele formation are also genetically predisposed to either hypercholesterolemia (Shetland Sheepdog) or hypertriglyceridemia (Miniature Schnauzer). The prevalence of hypercholesterolemia among dogs with mucocele formation ranges from 41% to 55% and hypertriglyceridemia from 43% to 54%. There is no significant correlation

between cholesterol and triglyceride concentrations in dogs with mucocele formation and only approximately 14% of dogs have both disorders, suggesting that cholesterol and triglyceride elevations may not share the same pathogenesis.

It seems prudent to consider the same diagnostic and treatment approaches to hyperlipidemia in dogs with mucocele formation as would be applied to dogs without mucocele formation. At a minimum, transitioning dogs to a fat-restricted diet is commonly recommended.

Proteinuria

A significant association between gallbladder mucocele formation and incidence of proteinuria in dogs has been documented.[22] The presence of proteinuria appears unrelated to concurrent diagnosis of hyperadrenocorticism, hypothyroidism, or hypercholesterolemia. Assessment of proteinuria is warranted in dogs with mucocele formation. Moreover, occult gallbladder mucocele formation should be considered as a possible differential diagnosis for proteinuria in dogs of predisposed age and breed. Diagnostic and treatment approaches to proteinuria in dogs with mucocele formation are like those for dogs without mucocele formation.

Imidacloprid in Shetland Sheepdogs

A matched case-control study[38] investigating any association between histologic diagnosis of mucocele formation and reported use of drugs for flea and tick infestation, heartworm prophylaxis, or degenerative joint disease found that Shetland Sheepdogs with mucocele formation were 9 times as likely to have had reported use of imidacloprid as were control Shetland Sheepdogs (95% CI, 1.103 to 78.239). This association was not observed in non–Shetland Sheepdog breeds. The results of this study do not suggest that imidacloprid is a primary cause of mucocele formation in dogs but possibly a contributing or exacerbating factor in Shetland Sheepdogs. Due to the possibility that imidacloprid is a contributing factor to mucocele formation in Shetland Sheepdogs, choice of an alternative flea and tick preventative in this breed seems warranted.

Medical Management as an Alternative to Surgery

Medical management of gallbladder mucocele formation as an alternative to surgery is controversial. It is unclear to what extent the progression of mucocele formation can be ameliorated or reversed. Reported median survival time of 33 dogs undergoing medical management was 1,340 days compared to 1,802 days in 46 dogs managed surgically. Median survival time was significantly decreased to 203 days in a group of 10 dogs that underwent medical management prior to surgery, although the circumstances leading to surgery in this group may have been associated with a greater number of risk factors.[24] Situations where medical management of dogs with gallbladder mucocele formation might be considered are (1) an asymptomatic patient with incidental finding of an "early mucocele" (ie, a gallbladder in which a significant portion of the contents remain liquid or gravity dependent) and (2) any patient having a nonruptured mucocele for which surgery is declined by the owner or otherwise not an option. Medical management of a mature gallbladder mucocele (ie, effacement of the gallbladder lumen by solidified mucus) is not recommended. Total or partial resolution of mucocele formation has been reported in only a handful of dogs.[39]

Treatments administered to these dogs have consisted of various combinations of fat-restricted or hypoallergenic diet, ursodeoxycholic acid, S-adenosylmethionine, silymarin, ω-3 fatty acids, and antibiotics. In 2 dogs, a concurrent diagnosis of hypothyroidism was treated with levothyroxine. All medically (and surgically) managed dogs should be evaluated and treated, if possible, for concurrent illnesses as outlined in the prior section.

Dogs with early mucocele formation and managed medically in attempt to avoid surgery should undergo periodic gallbladder ultrasound to evaluate disease progression. The frequency of ultrasound examinations should be based on the initial severity of mucus consolidation, pace of apparent accumulation, and aversion to risk of unanticipated rupture. A conservative starting interval would be a first recheck ultrasound 1 to 2 months following diagnosis, with subsequent intervals based on findings.

In the authors' experience, dogs with mucocele formation are prone to secondary bacterial cholecystitis. Therefore, in medically managed cases that present with clinical signs of gallbladder disease, an inflammatory leukogram, elevated liver enzyme activities and total bilirubin, or ultrasonographic evidence of cholecystitis of any type, the authors will treat with broad-spectrum antibiotics (fluoroquinolone and [metronidazole or amoxicillin-clavulanate]) for a duration of 2 to 4 weeks.

Summary

Gallbladder mucocele formation is an important differential diagnosis to consider in older, small-sized dogs of predisposed breed that present with acute clinical signs of gastrointestinal illness and serum biochemical evidence of hepatobiliary disease. Abdominal ultrasound is necessary for definitive diagnosis. Considerable variation in the ultrasonographic appearance of mucocele formation and poor sensitivity of ultrasound for detection of infarction or rupture remain significant challenges for diagnosis, gauging disease severity, and clinical decision-making. Importantly, the clinical presentation of mucocele rupture often differs from classical gallbladder rupture, as many dogs with ruptures have neither bile peritonitis nor hyperbilirubinemia because the rupture may leak mucus rather than bile into the abdominal cavity.

Asymptomatic dogs undergoing elective cholecystectomy have a better prognosis than those undergoing surgery after the onset of clinical signs. There is minimal evidence for effectiveness of medical management alone in reversing mucocele formation. Medical management to specifically address concurrent disease is an important consideration in

all dogs with mucocele formation. This might include changes in diet to address concurrent illnesses, hepatoprotective supplements, and treatment of concurrent endocrinopathy, hyperlipidemia, proteinuria, and, in some cases, suspected or documented biliary bacterial infection.

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