Biliary Mucoceles: When to cut, and why
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Lecture Outline
- Biliary mucocele etiopathogenesis
- Biliary mucocele clinical presentation
- Biliary mucocele diagnosis
- Surgical management of biliary mucoceles
- Medical management of biliary mucoceles
- Case selection: When to consider medical management, and when to recommend surgery

Biliary Mucocele Etiopathogenesis
- Definition of biliary mucocele: A mucous filled distension of the gall bladder with associated dysfunction of the gall bladder
- Histopathology of the gall bladder wall of patients with biliary mucocele reveals cystic mucinous hyperplasia
- Progressive distension of the gall bladder wall results in ischemic necrosis of the gall bladder wall, which causes gall bladder rupture
- While mucin is originally produced in the gall bladder, it can eventually enter and obstruct the extrahepatic biliary tree, causing progressive distension and devitalization of the extrahepatic biliary tree
- Many pathogenesis have been reported in the literature
- Gall bladder rupture is common (up to 50% of biliary mucocele cases that go to surgery)
Biliary Mucocele Etiopathogenesis

- Hypothesis 1: Chronic inflammation of the gall bladder leads to increased mucin production and resultant hyperplasia of mucous secreting cells
  - Histopathology of the gall bladder of dogs with documented mucoceles does not universally reveal inflammation
  - Those cases that do have inflammation of the gall bladder wall typically have necrotic areas of the wall immediately adjacent to the inflammation (suggesting that the inflammation is a secondary problem, rather than the primary cause of mucocele formation).

- Hypothesis 2: Structural obstruction of the cystic duct or common bile duct causes mucocele formation
  - Well documented to be highly associated in humans with biliary mucocele
  - The majority of dogs with biliary mucocele do not have evidence of a primary obstructive process, although many will have secondary extrahepatic biliary obstruction due to the presence of mucocele in the common bile duct or hepatic duct
  - Experimental ligation of the cystic duct of dogs did not result in mucocele formation at the time of necropsy 4-10 weeks post-ligation

- Hypothesis 3: Biliary mucocele formation is a complication of dyslipidemia
  - A large number of dogs with biliary mucocele also have hypertriglyceridemia and/or hypercholesterolemia
  - Many of the breeds predisposed to biliary mucocele are also predisposed to disorders of lipid metabolism (e.g. Miniature Shnauzer, Cocker Spaniel, Shetland Sheepdog)
  - Many dogs with biliary mucocele have concurrent endocrinopathies which are known to result in disorders of lipid metabolism (e.g. hyperadrenocorticism, hypothyroidism)
**Hypothesis 4**: Biliary mucocele formation is a complication of certain endocrinopathies
- Hyperadrenocorticism has been shown to increase the odds of biliary mucocele by 29 times
- Hypothyroidism has been shown to increase the odds of biliary mucocele by 3 times (although possible observation bias was reported in the same study)
- Proposed mechanisms:
  - Hypothyroidism has been shown to cause increased tone of the Sphincter of Oddi
  - The administration of progestogens to prairie dogs has been shown to decrease the rate of gall bladder emptying in response to cholecystokinin and also has been shown to increase tone of the Sphincter of Oddi
  - High progesterone levels have been shown to be associated with cystic mucinous hyperplasia of the gall bladder
- There has been no association shown between biliary mucocele and diabetes mellitus

**Hypothesis 5**: Biliary mucocele formation results from biliary dysmotility
- Biliary dysmotility leads to prolonged exposure of the biliary epithelium to bile acids
- Chronic exposure of the biliary epithelium to bile acids results in injury to the epithelial lining
- Cystic mucinous hyperplasia is a universal sequela of epithelial injury

**Hypothesis 6**: Mutations in the gene ACBC4 predispose patients to the development of biliary mucocele
- ABCB4 encodes for a phosphatidylcholine transporter (i.e., it enables phosphatidylcholine to enter the biliary tree across the biliary epithelium)
- Phosphatidylcholine protects the epithelial cell membranes from the cytotoxic detergent effects of bile
- If there is less phosphatidylcholine present, then cellular injury due to exposure to bile salts is worse, resulting in cystic mucinous hyperplasia (universal response to epithelial lining)
- In humans, mutations in ACBC4 are associated with intrahepatic cholestasis of pregnancy, progressive familial intrahepatic cholestasis, primary biliary cirrhosis, and cholestasis
- In humans, the degree of disease is worse in patients whose ABCB4 mutations result in lower quantities of phosphatidylcholine being formed
- In one study, dogs with biliary mucocele were found to have an insertion mutation in ABCB4, which reduced its function by 50%
Biliary Mucocele Clinical Presentation

- Most commonly reported breeds: Cocker Spaniel, Shetland Sheepdog, Miniature Schnauzer
- Patients are usually mid-aged to older
- No sex predisposition
- Most commonly reported clinical signs: anorexia, lethargy, vomiting, diarrhea, abdominal pain (ie. Non-specific clinical signs).
- Many dogs (23% in one study) have no clinical signs of hepatobiliary disease (these patients are being evaluated for clinicopathologic abnormalities)

Biliary Mucocele Clinical Presentation

- Physical examination findings: Abdominal pain, icterus, hyperthermia
- NOTE: Many dogs with biliary mucocele have no abnormalities on physical exam
- Most common laboratory abnormalities: increases in alkaline phosphatase, alanine aminotransferase, gamma glutamyltransferase, increased total bilirubin; increased cholesterol, increased triglycerides, increased white blood cells.

Biliary Mucocele Diagnosis

- Abdominal ultrasound is by far the most common tool used to diagnose biliary mucocele.
- Two classic gall bladder appearances are described:
  1. Striated bile pattern with lack of bile mobility
  2. Stellate bile pattern with lack of bile mobility
- Signs of gall bladder rupture:
  - Discontinuous gall bladder wall
  - Presence of pericholecystic fluid
  - Presence of peritoneal effusion
  - Presence of stratified hyperechoic material (mucocele) within the abdominal cavity

- Elevations in hepatic enzyme activities, total bilirubin, and white blood cell counts tend to be higher in patients with gall bladder rupture

No one laboratory abnormality is seen in every case of biliary mucocele.
Biliary Mucocele Diagnosis

- In a recent study, 1/3 of patients with biliary mucocele documented at surgery did NOT have strong ultrasonographic evidence of biliary mucocele.
- Many cases with evidence of current or previous biliary leakage at surgery do not have evidence of peritonitis on ultrasound (studies disagree on the sensitivity of ultrasound for bile leakage).

Biliary Mucocele: Surgical Management

- Surgical approaches discussed in the literature:
  - Cholecystectomy
  - Choledochoduodenostomy (no longer recommended)
- There is a high rate of extrahepatic bile duct obstruction due to gelatinous bile in the common bile duct + hepatic ducts.
- Recommend antegrade or retrograde flushing to remove this obstructive material.
- Some studies suggest that, even in cases with obstructed extrahepatic biliary tree, cholecystectomy alone is sufficient (ie. No flushing of the extrahepatic biliary tree is performed, and patients do well despite this).

Biliary Mucocele: Surgical Management

- Surgical mortality rate is variable dependent on the study, ranging from 21% to 40%.
- Most studies suggest no difference in survival between patients with gall bladder rupture vs. patients with an intact gall bladder wall.
- There does appear to be a significant difference between patients with extrahepatic bile duct obstruction and those without (0%-13% mortality).
- Studies do not agree on the infection rate in patients with biliary mucocele—range from 9% to 44%.
- Part of the reason for variability may be pre-operative antibiotic therapy.
- Most studies do agree that infection does not seem to be a primary cause of biliary mucocele, but rather a consequence of biliary mucocele.
  - Complications: Pulmonary thromboembolism, aspiration pneumonia, severe pancreatitis, bile peritonitis, SIRS, sepsis.
Biliary Mucocele: Surgical Management

- In a recent study, increased post-operative lactate levels and hypotension in the early post-operative period were found to be negative predictors of survival.
- A different study reported that hypokalemia and more severe neutrophilia were negative predictors of survival.
- Patients that survive the perioperative period have a good prognosis (66% 2 year survival).
- Almost all patients have concurrent intrahepatic disease of varying severity.
  - Portal hepatitis and fibrosis with bile ductule proliferation is the most common finding, but neutrophilic cholangitis and lymphoplasmacytic cholangitis are also reported.

Biliary Mucocele: Surgical Management

- The role of laparoscopic cholecystectomy:
  - Only reported in 6 cases, all of which had uncomplicated biliary mucocele (ie. No evidence of gall bladder rupture and/or bile peritonitis)
  - All cases did very well, with no intraoperative or post-operative complications.
  - For the moment, best used in uncomplicated cases (ie. no strong evidence of extranepatic bile duct obstruction or bile peritonitis).
  - Main concern, even in uncomplicated cases, is the inability to assess and/or flush the common bile duct via laparoscopy.

Biliary Mucocele: Medical Management

- Antibiotics: Choose broad spectrum, with good coverage for enteric organisms.
  - Ideally, obtain a bile sample for culture via cholecystocentesis PRIOR to starting antibiotics.
- Ursodiol: Many mechanisms of action—choleretic effects, anti-apoptotic effects, immunomodulatory effects, replacement of more toxic bile acids, anti-oxidant effects.
- SAM-E: Antioxidant effects, proposed to have additive effects when used along with ursodiol.
- Not much literature is available describing medical management of biliary mucocele—one paper describes successful medical management in 2 cases, another paper describes successful medical management in 1 case.
- Some of the patients successfully managed medically had massive bile duct enterocutaneous fistulae, and all of them had relatively few clinical signs associated with biliary mucocele.

Contents of a biliary mucocele
Biliary Mucocele: One Clinician’s Approach

- Discuss surgical management of biliary mucocele with all owners, regardless of whether their dogs are showing clinical signs.
  - Rationale: The high post-operative mortality rates in the literature suggest that waiting until a patient is showing clinical signs may yield a worse short-term prognosis.
- Consider laparoscopic cholecystectomy in cases that are showing no clinical signs, have no dilation of the common bile duct on ultrasound, and have no ultrasonographic or clinicopathologic evidence of gall bladder rupture.
- Consider medical management with antibiotics, ursodiol, and SAM-E in patients who are non-clinical for biliary mucocele or who have concurrent disease which makes them poor surgical candidates.
  - CLOSE monitoring is essential in these patients, with ultrasounds and repeat bloodwork every 4-6 weeks.
- STRONGLY recommend surgery (laparotomy) in cases that have significant clinical signs referable to biliary mucocele, any evidence of gall bladder rupture, or progressive changes on ultrasound or bloodwork.

References


Questions???