

Gallbladder Mucoceles in Shetland Sheepdogs

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Gallbladder mucocele formation is a relatively uncommon problem in dogs that results in inflammation and possible rupture of the gallbladder wall. Clinical signs of affected dogs include vomiting, loss of appetite, and abdominal pain. Without surgical removal of the gallbladder, the dog may die if rupture occurs. Many other diseases cause similar clinical signs, and because gallbladder mucoceles are relatively uncommon, the diagnosis can be missed or delayed. The diagnosis is usually made via ultrasound examination (Figure 1), exploratory surgery, or on necropsy. The Shetland Sheepdog is one of the breeds that is predisposed to the problem.¹

In 2008, Katrina Mealey, DVM, Ph.D. of the College of Veterinary Medicine, Washington State University, began searching for a genetic mutation that might be a contributory factor in the formation of gallbladder mucoceles in Shelties. The American Shetland Sheepdog Association played an integral part in soliciting DNA samples from affected and unaffected (control) Shelties. Owner participation was outstanding and within 18 months of the time the ASSA joined the effort, Dr. Mealey received enough DNA samples to help her identify the mutation. Her work was published in 2010 and is available online.²

Brief review of the anatomy and physiology of the biliary tree and bile

Bile is produced in the liver to aid in the digestion of food in the small intestine. Liver cells (hepatocytes) excrete bile into a tree-like system of branched ducts (bile ducts) within the liver. These ducts gradually coalesce into a large duct that extends between the liver and the small intestine. The gallbladder is an oval shaped sack-like structure that extends from the large bile duct via a short “cystic” duct. The gallbladder acts as a reservoir to store and concentrate bile between meals as some bile exiting the liver via the large bile duct enters the gallbladder. When food enters the intestine, the gallbladder is stimulated to contract, thus depositing bile into the intestine.

Probable mechanism for gallbladder mucocele formation in Shelties²

Bile salts are one of the components of bile. They have an important function in digestion of food; however, they are toxic to the cells lining the biliary tree and gallbladder. Phospholipids are another component of bile, and they have an important protective effect on the cells lining the biliary tree and the inner wall of the gallbladder. A specific protein (called ABCB4) within the hepatocyte cell membrane is essential for the transfer of phospholipids from the hepatocyte and into the bile ducts. If the amount of this ABCB4 protein is deficient or if its function is altered, inadequate amounts of phospholipids are transferred into the bile ducts. Without the protective effect of the phospholipids, the bile salts cause chronic irritation of the gallbladder wall. The gallbladder wall responds by producing mucin, a thick, gooey substance. Over time, the

gallbladder wall becomes inflamed and the mucin combines with the bile to form a thick semi-solid gelatinous mass (mucocele) within the gallbladder and its duct (Figures 1 & 2). Bile no longer can enter or exit the gallbladder and flows directly from the liver into the intestine. Eventually, the gallbladder wall may rupture, resulting in patient death. The mutant gene found in affected Shelties is responsible for the synthesis of the ABCB4 protein that transfers the phospholipids into the bile ducts.² The amount of ABCB4 protein within the hepatocyte cell membrane is then insufficient to transfer enough protective phospholipid into the bile ducts.

In general, this appears to be a disease of older dogs. In Dr. Mealey's report, Shelties with confirmed gallbladder mucoceles had clinical signs that prompted owners to seek veterinary help. The average age of affected dogs was 9 years (range 5 – 12 years). Since the report was published, one affected 3-year-old Sheltie was discovered (Dr. Mealey, personal communication). Fourteen of the 15 affected Shelties tested and all 3 affected dogs of other breeds had one copy of the mutant gene. Only 1 of 21 unaffected shelties had the mutant gene. Since all affected dogs were heterozygous for the mutant gene, a dominant mode of inheritance with incomplete penetrance was suggested. None of the dogs was homozygous for the mutation.

This mutant gene is not likely to be the only factor in gallbladder mucocele formation in dogs, but it appears to be the major contributory factor in Shelties. A commercially available DNA test will help breeders eliminate the mutation from the Sheltie population. Dr. Mealey is working to develop a DNA test that is accurate and affordable. The method used to identify the mutant gene during the research phase is difficult, time consuming, and expensive.

Once a DNA test becomes commercially available, work can be initiated to answer several questions:

- 1) What percent of Shelties (and dogs of other breeds) carry the mutation?
- 2) What happens to dogs with two copies of the mutation? Perhaps, these dogs have a more severe form of the disease that results in death either during embryonic development or in the perinatal period.
- 3) What percent of dogs with one copy of the mutant gene develop gallbladder mucoceles? (It may be 100% if the dogs live long enough.)
- 4) If dogs with one copy of the mutation are identified early and then followed with periodic ultrasound examinations, at what age do the mucoceles form?
- 5) What percent of dogs diagnosed with mucoceles prior to onset of clinical signs develop clinical problems necessitating surgical removal of the gallbladder?
- 6) What treatment, if any, should be undertaken for young dogs with the mutant gene? Should such dogs be treated prophylactically with drugs that make the bile

thinner? For instance, we might learn that medical treatment should be instituted when the dogs are a certain age, ex. 4 -5 years old.

- 7) Should dogs at risk for gallbladder mucoceles receive periodic ultrasound examination, and if so, beginning at what age and how often?
- 8) Would periodic blood tests be indicated for at risk dogs?
- 9) Should the gallbladder be removed in asymptomatic dogs with gallbladder mucoceles? This has been recommended in one report.¹
- 10) Should the normal gallbladder of dogs with the mutant gene be removed at an early age? For example, when a female carrying the mutant gene is spayed, should the gallbladder be removed at the same time?
- 11) Are the bile ducts within and outside the liver adversely affected or is the gallbladder the only structure adversely affected?

What do Sheltie owners do while waiting for a commercially available DNA test?

If you are unaware of any affected dogs in your dog's pedigree, then inform your veterinarian of the possibility of gallbladder mucocele formation if your dog develops any of the above mentioned clinical signs. The information we now have concerning Shelties is very new and not widely known in the veterinary community.

If you know that an affected dog exists in your dog's pedigree –

- Inform the dog's veterinarian that the dog may be at risk for gallbladder mucocele formation. Again, mucoceles are uncommon and most veterinarians are unaware of the newly found mutant gene in some Shelties. Corticosteroid therapy and Cushing's disease may also be risk factors in development of gallbladder disease,^{1,3} so veterinarians may want to take these factors into consideration when treating at risk dogs.
- One could consider prophylactic medical therapy as noted above (#5) before mucocele formation begins. If the dog develops clinical signs consistent with mucocele formation, the veterinarian can include that on the rule out list as a possible cause. Normal liver function tests results may not rule out the presence of a gallbladder mucocele.
- Consider periodic ultrasound examination of the gallbladder starting at 5 to 8 years of age. The examination must be performed by a veterinarian experienced in recognizing gallbladder mucoceles. Sludge within the gallbladder is a common finding in "normal" dogs and should not be confused with mucocele formation. In general, board certified radiologists and internal medicine

veterinarians are competent at making the diagnosis. Some general practitioners are also very experienced and capable of making the correct diagnosis.

- If your dog is diagnosed with a gallbladder mucocele, discuss the options with your veterinarian. Considerations include: 1) prophylactic gallbladder removal, 2) no action unless clinical signs develop, and 3) medical therapy. One study of gallbladder disease in 38 Shelties found that gallbladder mucoceles could be subclinical, but quickly result in acute illness.¹ In 11 Shelties, gallbladder disease was found serendipitously indicating that dogs may not have clinical signs of disease during mucocele development. Mucoceles were confirmed in 25 of 38 Shelties included in the report. The authors recommended gallbladder removal in asymptomatic dogs with mucoceles because of low survival rate of clinically affected dogs. In one dog, a mucocele resolved 6 months after medical treatment (with ursodeoxcholic acid) and a fat-restricted diet; there was no change in mucoceles of 2 other dogs treated similarly.

Figures 1 and 2 are ultrasound and gross images a gallbladder and mucocele removed from an asymptomatic 8-year-old Sheltie. The owner had 2 full siblings sired by an affected dog. Both dogs were clinically normal, but received ultrasound scans as a screening measure since they were at an age where mucocele formation might occur and the sire was known to have been affected. Each dog had a 50:50 chance of having a gallbladder mucocele. One was normal, the other had a mucocele. Even though the affected dog was clinically normal and the blood work was also normal, the owner elected to have the gallbladder removed. The gallbladder was moderately distended and filled with a gelatinous, semi-solid material. The dog recovered uneventfully.

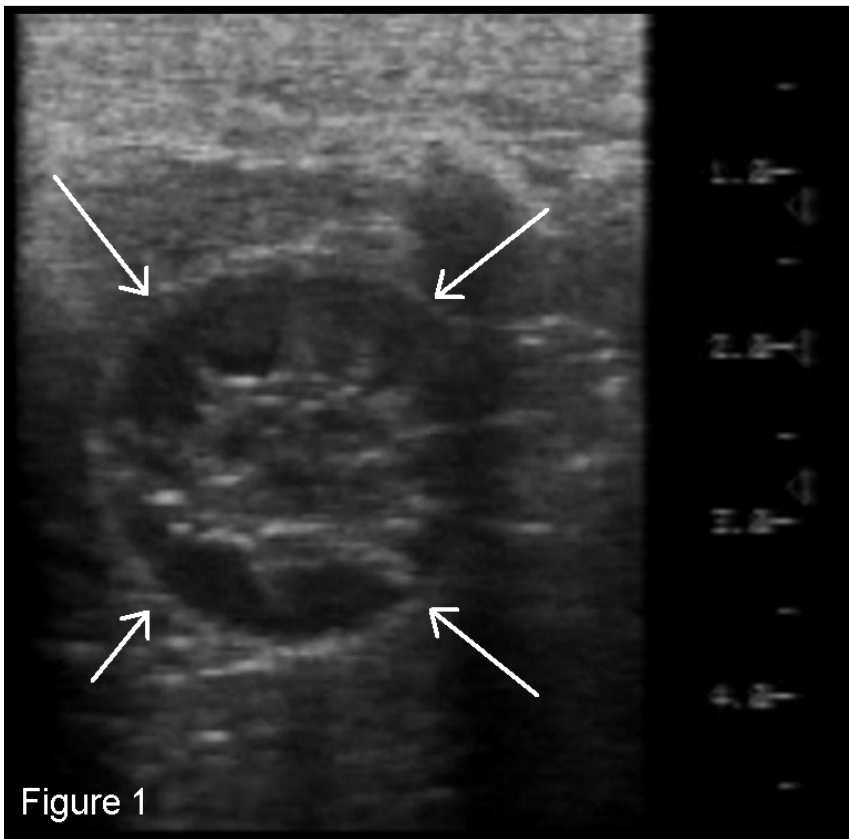


Figure 1: Ultrasound image of the gallbladder (arrows) of an asymptomatic 8-year-old Sheltie with a gallbladder mucocele. The mucocele appears as a stellate-shaped gray object within the gallbladder. The

inside of a normal gallbladder would be uniformly black.

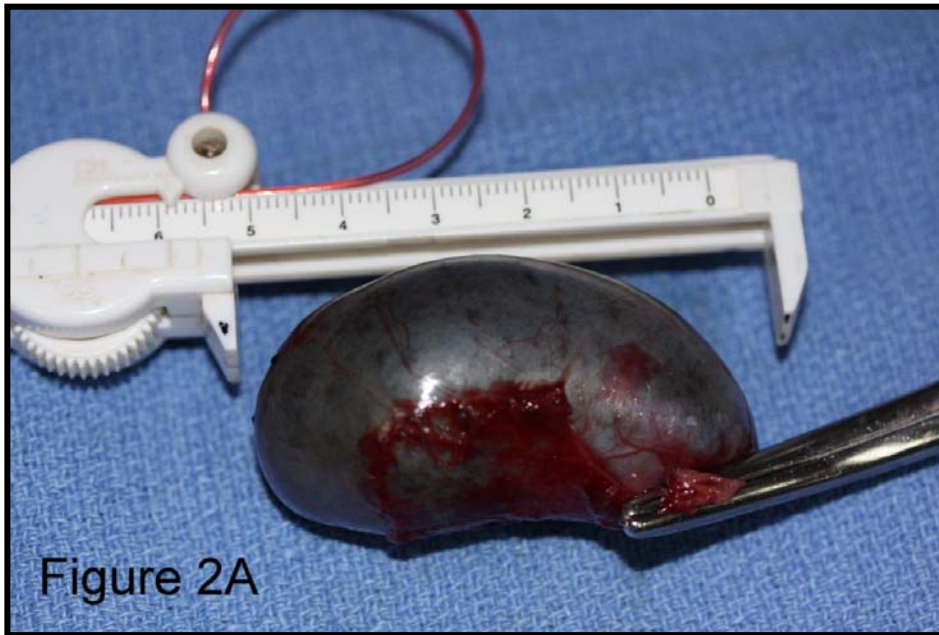


Figure 2:
The photos of a gallbladder and mucocele removed from the same Sheltie as in Figure 1.
(A) Intact gallbladder shortly after

surgical removal. The gallbladder is distended.



Figure 2B: An incision has been made along the long axis of the gallbladder revealing the gelatinous mass of the mucocele.

In a normal dog, the gallbladder would have collapsed and the fluid contents spilled onto the towel when incised.

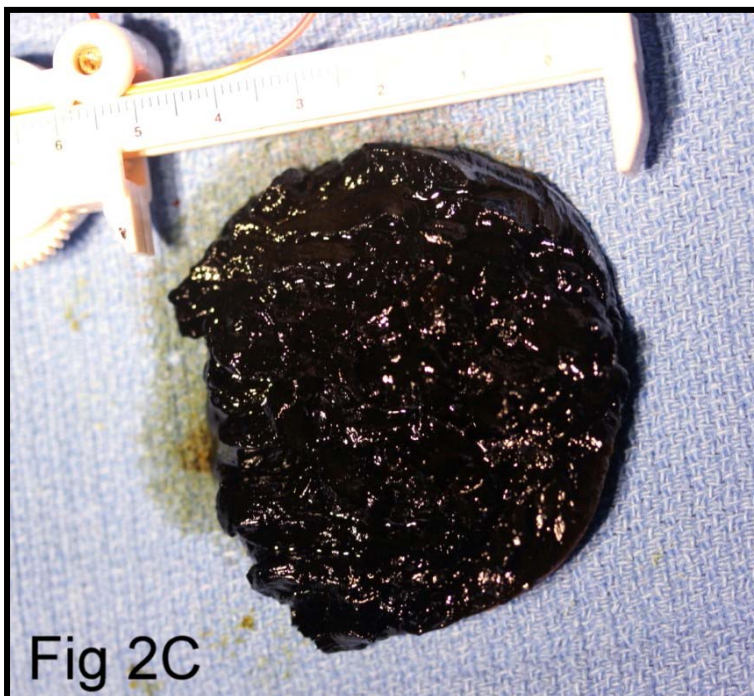


Figure 2C: The gallbladder and mucocele have been cut in half.

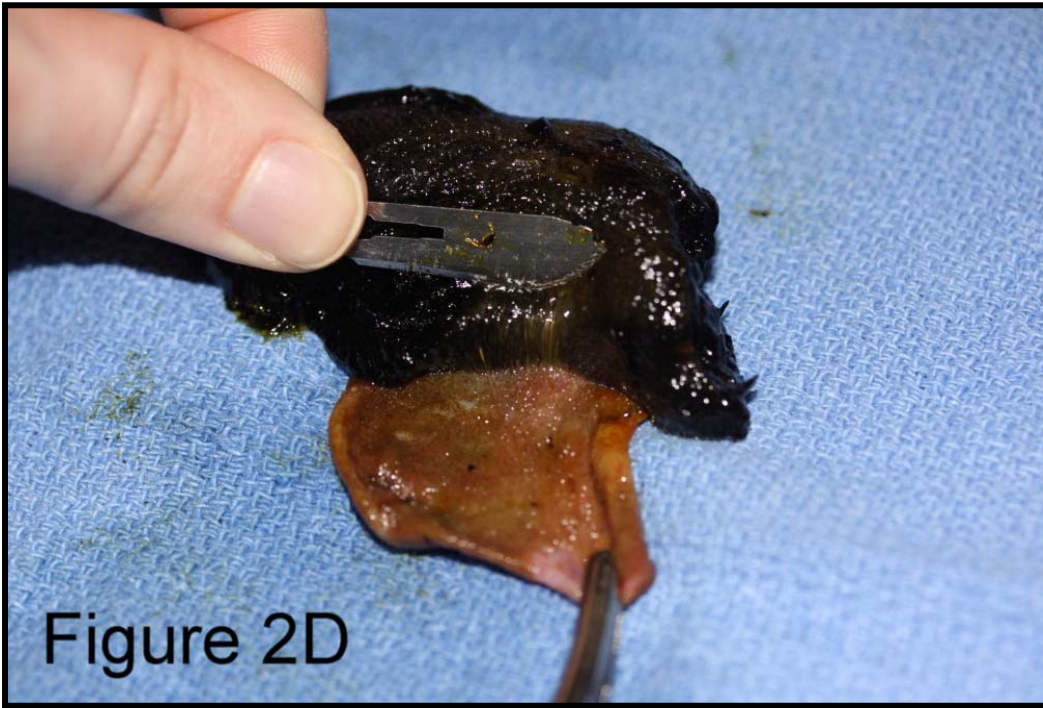


Figure 2D: Mucocoele being peeled away from the gallbl

adder wall. The mucocoele was tightly adhered to the gallbladder wall.

It is not known how long the mutant gene has been in the Sheltie population. The clinical signs associated with mucocoeles are common to other diseases, so some dogs with mucocoeles may have been misdiagnosed, especially prior to the use of ultrasound in veterinary medicine. Also, many dogs are elderly when clinical signs occur. These dogs

often have other medical problems, so expensive diagnostic tests may not have been pursued. Some carriers may have died from other causes before gallbladder mucoceles could result in clinical signs.

Since the problem is one of older dogs, dogs will have been bred and produced offspring long before the diagnosis is made. As noted above, a commercially available DNA test will aid breeders in eliminating the mutation from the population while retaining the desirable genes of those dogs and maintaining genetic diversity within the breed. Carriers should be bred to non carriers, so as to eventually select for non carriers with the most desirable traits. Each pup from such a breeding would have a 50:50 chance of being normal (non carrier). Geneticists generally do not recommend immediate culling of carrier dogs in order to maintain genetic diversity and to avoid a genetic “bottle neck” of other potentially undesirable traits.⁴ Thanks to the efforts of Dr. Mealey and her colleagues and to those owners who participated in the study, breeders will eventually have the knowledge needed to decrease the incidence of gallbladder mucoceles in the breed.

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