

The Gallbladder Halo Sign: Update on the Diagnosis & Complications of Canine Anaphylaxis

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INTRODUCTION

The lecture will not cover detail regarding the pathophysiology of anaphylaxis of which there exist many excellent published descriptions. Rather, the lecture will focus on how to rapidly gain supportive evidence for the diagnosis of canine anaphylaxis, including the sonographic marker of gallbladder wall edema; and important rule outs for sonographically-detected gallbladder wall edema that can confound the diagnosis at the expense of the patient; and a newly described fascinating complication referred to by the author as canine "anaphylaxis-related, heparin-induced hemoabdomen" that is medically-treated.

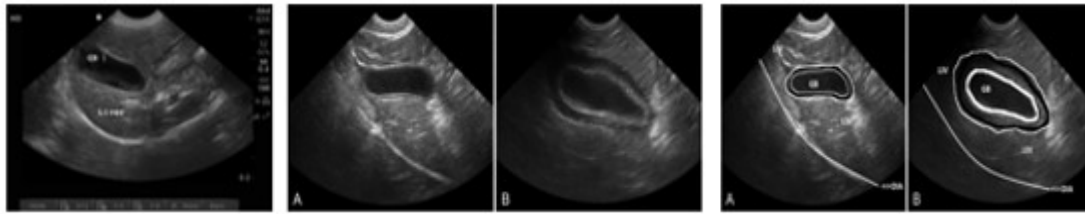
The major reason for this lecture is that many veterinarians are now using point-of-care ultrasound, specifically FAST exams, as a life-saving, first-line, screening test. As a result, ultrasound detects free-fluid and other soft tissue changes that are not recognized without ultrasound; and many triaged collapsed dogs with anaphylaxis have no cutaneous signs nor witnessed inciting envenomation. The focus of the source of anaphylaxis in this lecture disregards the obvious canine with classic cutaneous signs of angioedema, pruritus, and urticaria, but focuses on the single Hymenoptera envenomation that is often unwitnessed. All veterinarians need to recognize the strengths and limitations of sonographically-detected gallbladder wall edema since its presence is not pathognomonic; and that AX-related, heparin-induced hemoabdomen is a medically treated canine complication, because without this knowledge gallbladder wall edema will be misinterpreted and surgical intervention will likely lead to a fatal exploratory surgery with the findings of hepatic swelling, intra-abdominal blood, and non-specific histopathology.

THE FAST DIAPHRAGMATICO-HEPATIC (DH) VIEW

Imaging the Gallbladder and Detecting Intramural Edema

In normalcy, the gallbladder sonographically is generally oval in longitudinal (sagittal) orientation with a lumen that is homogeneously anechoic (black). The gallbladder wall is quite reliably and seen sonographically as a thin hyperechoic (white) line in both canines and felines despite normal thickness reported to a thickness of 2–3 mm. In summary, the sonographic features of the canine and feline gallbladder are easy to appreciate by non-radiologist sonographers when imaging the FAST DH view. In a 2009 study, Quantz *et al.* published in JVECC a brilliant study that correlated the presence of a thickened, edematous, striated gallbladder wall, referred to as the gallbladder halo sign, with canine anaphylaxis (AX). Their study design was a result of recognizing that in a canine AX research model, gallbladder wall edema was commonly present.

Figure 1



Normal expected sonographic appearance of the gallbladder wall in canines. Unlabeled middle figure with A and B shows more subtle gallbladder wall striation/intramural edema in A and more obvious gallbladder wall striation/intramural edema in B. Far right image is now outlined. This material is reproduced and modified with permission of John Wiley & Sons, Inc, Focused Ultrasound Techniques for the Small Animal Practitioner, Wiley ©2014.

Gallbladder Wall Edema as a Sonographic Marker for Canine Anaphylaxis (AX)

AX-related gallbladder edema is specific to canines because their shock organ, where the highest concentration of mast cells are located, is their liver and gastro-intestinal tract. In contrast, the shock organ of felines and humans is the lung, thus gallbladder wall edema is not a hallmark of AX in these species. The cause of gallbladder wall edema is the result of massive histamine release causing hepatic venous sphincter constriction and massive generalized hepatic venous congestion. Simply put, when the liver swells, so does the gallbladder wall. This is important to remember when considering other rule outs for canine gallbladder wall edema. The AX-related intramural gallbladder edema is recognized sonographically as sonographic striations. These striations appear as a hyperechoic (white) lines representing the inner and outer aspects of the gallbladder wall, and a sonolucent anechoic (black) line striation representing the intramural edema. In other words, the gallbladder wall becomes layered as white, black, and white, (sometimes it is white, gray, white), and thus has been dubbed the "gallbladder halo sign." In the Quantz *et al.* study, it was found that AX-induced gallbladder edema is an immediate occurrence within seconds/minutes that lasts up to 24–48 hours post-insult.

Serum Alanine Transaminase as a Serum Marker for Canine Anaphylaxis (AX)

Because the liver and gastro-intestinal tract are the shock organ for the canine species, traditionally serum alanine transaminase (ALT) has been used as supportive evidence for canine AX. However, in the Quantz *et al.* study, it was stated that serum ALT marker was not as immediate as gallbladder wall edema; and that the ALT may not spike in value for up to 2–4 hours post-insult. Quantz *et al.* documented a mean ALT of ~400 IU/L for their case study population of canine AX.

The Classic Constellations of Signs for Canine Anaphylaxis

Keeping in mind the canine shock organ, traditional means of diagnosing anaphylaxis have relied on a history of acute collapse often associated with gastro-intestinal signs in a previously healthy dog. The collapse is often associated with gastro-intestinal signs (i.e., vomiting and defecation). The great majority of these dogs have no obvious cutaneous signs. Upon presentation due to massive fluid shifts caused by histamine release and likely other factors that increase vascular

permeability, dogs with AX are commonly hemoconcentrated with packed cell volumes in the 50% range and even higher (in contrast dogs with a hemoabdomen from a bleeding tumor are not hemoconcentrated); and as previously mentioned, the serum ALT is likewise a marker because of the hepatic insult. The weather should also be considered because many warm days and cool nights make Hymenoptera species lethargic and less likely to move away from the dog walking and sniffing in the grass in the cool evenings and mornings (author's experience).

Gallbladder Wall Edema is Not Pathognomonic for Canine Anaphylaxis - It's also a "Cardiac Gallbladder"

In the collapsed or acutely weak hypotensive canine triaged with the finding of gallbladder wall striation/edema, other important rule outs include pericardial effusion, right-sided heart and generalized systolic dysfunction (DCM). The pathophysiology of gallbladder wall edema in these cases is mechanical obstruction of blood, in which backflow of blood leads to a distended caudal vena cava (CVC), and hepatic venous congestion. Simply put, when the liver swells, so does the gallbladder. These rule outs are addressed by looking past the diaphragm for pericardial effusion, the classic racetrack sign of pericardial effusion rounding the muscular apex of the heart; and adding the right TFAST pericardial (PCS) view to assess contractility at the left ventricular short-axis view. Moreover, the really savvy sonographer always, always looks at the caudal vena cava (CVC) where it traverses the diaphragm at the FAST DH view. The CVC is a marker for central venous pressure (CVP) and its human counterpart, the inferior vena cava at the analogous location, is being taught to medical doctors. The CVC in AX is flat (no volume, low CVP) with no variation in its diameter vs. the CVC characterization in pericardial effusion and cardiac cases is diametrically opposed as FAT (too much volume, high CVP), or distended with minimal variation in its diameter. When the CVC is FAT from a high CVP, hepatic veins, not normally obvious in lateral or standing/sternal recumbency, are obvious branching structures from venous downstream obstruction. The upshot is that gallbladder wall edema is not pathognomonic for canine anaphylaxis in the collapsed or weak canine; that veterinarians must resist satisfaction of search error and minimally look past the diaphragm for pericardial effusion and the TFAST right PeriCardial View to evaluate contractility before administering large volumes of crystalloids.

Figure 2



The gallbladder halo sign and FAT (distended) CVC in a dog with pericardial effusion (PCE) in A and B. PCE should be ruled out in collapsed, weak dogs suspected of having AX. The single figure on the right showing the FAT (distended) caudal vena cava (CVC) as it traverses the diaphragm (DIA); and the associated distended branching hepatic veins appearing as tree

trunks (referred to as the tree trunk sign). The character of the CVC is completely different between canines with AX (flat CVC) and canines with pericardial effusion or right-sided heart failure/DCM (FAT CVC). LV: left ventricle; RV: right ventricle; PCE: pericardial effusion; DIA: diaphragm; GB: gallbladder; CVC: caudal vena cava; FF: free abdominal fluid. This material is reproduced with permission of John Wiley & Sons, Inc, Focused Ultrasound Techniques for the Small Animal Practitioner, Wiley ♦ 2014.

Causes of gallbladder wall edema (the gallbladder halo sign)

Anaphylaxis (acute collapse, flat caudal vena cava) - massive histamine release results in hepatic venous congestion
Right-sided heart failure/dysfunction (collapse, weakness, FAT caudal vena cava) - backflow of blood to the right heart results in hepatic venous congestion
Pericardial effusion (acute collapse, weakness, FAT caudal vena cava) - obstruction of blood flow to the right heart results in hepatic venous congestion
Cholecystitis
Pancreatitis
Hypoalbuminemia, 3rd spacing
Right-sided volume overload (iatrogenic), from intravenous fluid therapy
Immune-mediated hemolytic anemia (IMHA), unknown cause, speculate immune-mediated
Post-blood transfusion, unknown pathogenesis, speculate immune-mediated, volume overload

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Other potential causes for gallbladder wall edema that are generally present in non-collapsed dogs include 3rd spacing from hypoalbuminemia and vasculitis, primary gallbladder disease including cholecystitis, pancreatitis, and iatrogenic right-sided volume overload. Gallbladder wall edema is often observed in dogs with in immune-mediated hemolytic anemia and post-blood transfusion. Its presence in these subsets of patients does not necessarily indicate canine AX, so it is important to look at the complete clinical profile of these canine patients.

Canine Anaphylaxis-Related, Heparin-Induced Medically-Treated Hemoabdomen

Dogs with anaphylaxis commonly develop abdominal effusion often scored as an abdominal fluid score (AFS) 1 or 2 using the AFAST-applied fluid scoring system; and most commonly

positive at the FAST DH view. These low-scoring effusions are often self-resolving, the canine patient is non-coagulopathic, and the volume too small for safely performing abdominocentesis. Serial AFAST with AFS, minimally one repeat AFAST 4-hours post-admission, is justified to detect worsening (increasing score) or resolution (decreasing score) of the AX-related effusion; and depending on clinical course, a repeat PCV/TS and coagulation profile; and AFAST with AFS again after daily patient rounds until the attending veterinarian is certain that AX has resolved. In fact, Global FAST - AFAST with AFS, TFAST, and Vet BLUE - is an even better format over AFAST alone because Global FAST provides information on volume status, lung status, and other potential complications occult by physical exam, blood and urine testing, radiography, and vital signs.

Other cases of canine AX have large volume effusions of AFS 3 and 4. Even in these large volume effusions, the coagulation profile may be close to normal and stay close to normal (<25% above baseline) on repeat PCV/TS and coagulation profile 4-hours post-admission along with AFAST with AFS. These large volume effusions will likewise generally self-resolve within 24-hours if the patient responds favorably to initial resuscitation and therapy for AX including fluid resuscitation ± epinephrine, histamine 1 blocker, histamine 2 blocker, and glucocorticoids. Abdominocentesis should be performed if the free fluid is safely accessible, generally at the most gravity-dependent regions of the abdominal cavity, when your patient is in lateral recumbency. In our experience, these effusions are hemorrhagic with a comparative abdominal PCV of minimally $\geq 50\%$ of the peripheral PCV. In canine AX cases with abnormal coagulation profiles, clotting factors should be replaced as soon as possible (e.g., fresh frozen plasma [FFP]). As a crude guideline, 1 in 5–7 canine AX cases require FFP, and 1 in 20 canine AX cases require pRBCs. Some of the coagulopathic canines require repeated FFP over several days. The author treats all canine AX cases with famotidine for several days and a 7-day tapering regimen of anti-inflammatory dosing of prednisone to attenuate the second wave of AX-related inflammation.

Pathophysiology of Canine AX-Related Heparin-Induced Medically-Treated Hemoabdomen

In theory, the aPPT is more affected by heparin, a natural component of the mast cell granule; thus, PT and aPTT times should be discordant with the aPTT far more prolonged than the PT (opposite of the warfarin or Coumadin effect). So when the PT is near normal or mildly elevated with an out of range aPTT, a flag should be raised that the coagulopathy is a result of AX and heparin and tryptase release by mast cells. However, the discordance seems unreliable and the entire clinical picture must be considered. In our case series of 11 dogs from nearly 4-years ago, all survived without surgery with complete resolution of their hemorrhagic effusion; and of the clients that responded to long-term follow-up, all 7 said AX had not recurred in their dog. The data from this case series is available off our FASTVet Facebook page or may be requested.

CONCLUSION

It is important to recognize the limitations and additional rule outs for the sonographic finding of a striated gallbladder wall, the so-called gallbladder halo sign; and that dogs have a unique AX-related, heparin-induced medically-treated hemoabdomen complication, and not over-react to stable patients with normal to relatively normal clotting times (<25% over baseline) since many

will self-resolve with standard AX therapy. In other words, many dogs with mildly abnormal coagulation profiles will resolve without transfusion products. Equally important is to know not to take an AX-related canine hemoabdomen to surgery, which could be catastrophic for the dog likely resulting in death. Larger case studies and more sophisticated coagulation assessment are needed to fully understand this perplexing canine AX-related phenomenon.

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SPEAKER INFORMATION

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