A Case Report of Acute Liver Failure

Presented By:

Ben Tomlinson

Mississippi State University

College of Veterinary Medicine

Advisor:

Alyssa Sullivant, DVM, MS, DACVIM

Clinicopathologic Conference

March 29th, 2019

Introduction:

The liver is among the most metabolically diverse organs of the mammalian body. Liver parenchymal cells perform an assemblage of functions which include "formation and excretion of bile during bilirubin metabolism; the regulation of carbohydrate homeostasis; lipid synthesis and secretion of plasma lipoproteins; control of cholesterol metabolism; formation of urea, serum albumin, clotting factors, enzymes and numerous other proteins; and the metabolism or detoxification of drugs and other foreign substances."[4] With this understanding, it is easy to see how hepatic insult could result in many chemical and metabolic troubles.

Acute liver failure is defined by a sudden insult to the liver, resulting in severe hepatic insufficiency and consequential drop in the maintenance of systemic homeostasis. While many definitions of acute liver failure exist in the veterinary literature, many sources separate it from chronic liver failure as the rapid onset of hepatocyte dysfunction in a patient without pre-existing liver disease. Acute liver failure may be further defined as separate from acute liver injury, in which hepatic function is sustained. Marked increases in serum liver enzymes and bilirubin concentration are some key manifestations of the acute liver failure process, as well as accompanying coagulopathy and encephalopathy. There are many causes of acute liver failure that include toxins, neoplasia, drug-induced hepatopathy, infectious agents, trauma, autoimmune disease, and even heat injury, but in some cases the exact cause of acute liver injury is unknown.

Acute liver disease is much less common than chronic hepatitis. Low-grade, chronic liver disease may go unnoticed for a considerable amount of time before clinical signs of acute disease manifest. The initial signs such as anorexia, vomiting and depression are often non-specific, but eventually progress to more severe signs of disease such as jaundice, ascites, hepatic encephalopathy and coagulopathy. Once enough inflammation and necrosis has pushed the liver beyond its ability to repair, the continuation of these processes work to only perpetuate the disease state, encouraging the more severe clinical manifestations of disease. The timing and manifestation of such signs,

including their severity are all dependent on the underlying etiology. Although it is possible for recovery with intensive care, acute liver failure carries a poor prognosis. One study reports that only 14% of dogs hospitalized for acute liver failure will go on to be discharged. [9]

History and Presentation:

Dakota was an indoor 5-year-old spayed female German shepherd who presented to the MSU-CVM Internal Medicine service on 5/24/18 with a one-week history of lethargy, intermittent inappetence and vomiting. She was referred by her primary veterinarian, who on 5/23/18 noted increased liver enzymes and prescribed cephalexin and enrofloxacin, and also gave an injection of ceftiofur. Approximately one week prior to her presentation at MSU-CVM, the owners reported witnessing an episode of vomiting shortly after eating, after which Dakota became markedly lethargic. While the lethargy continued, she became intermittently inappetent and by the time of presentation at MSU-CVM, she had been anorectic for four days. The owner had tried offering baked chicken and rice, eggs, and also bacon to no avail. There were no potential exposures to liver toxins of which the family was aware.

Dakota had been seen at MSU-CVM several times in the past and had an extensive medical history, as detailed here. In November 2013, at 6 months of age, Dakota presented to her primary veterinarian for an ovariohysterectomy. Upon entering the abdomen, the veterinarian observed an enlarged and mottled spleen with numerous fibrous adhesions present between the spleen, small intestines, urinary bladder, and uterus. An attempt to break some of the adhesions from the uterus was made. However, a mild-moderate amount of bleeding occurred, and the surgery was terminated. She was then referred to MSU-CVM, where abdominal exploratory surgery and an ovariectomy was completed. At that time, multiple adhesions were found throughout the abdomen, most notably from the descending colon to the bladder. A sample of abdominal fluid was submitted for culture and no growth occurred. Although rare, sclerosing encapsulating peritonitis disease was suspected as these lesions are a hallmark complication of the disease.

In March of 2014 and at 10 months of age, Dakota returned to MSU-CVM on referral for a distended abdomen. Imaging revealed abdominal free fluid, dorsal displacement of the intestines, and adhesions encapsulating both the spleen and the kidneys. Abdominal fluid was collected and analysis revealed chronic hemorrhage without bacterial growth culture. Dakota was diagnosed with Sclerosing/Fibrotic Encapsulating Peritonitis and treated with prednisone and tamoxifen for 6 months.

In May of 2017 at one year of age, Dakota was brought to MSU CVM once again for a history of abdominal distention, fever, lethargy, and inappetence. A 20 cm cyst like structure on the left medial liver lobe was observed on ultrasound and Dakota was taken to surgery. In surgery, the cyst structure ruptured and was adhered to the spleen. The surgeons elected for a partial liver lobectomy and a splenectomy as the resulting adhesion would provide opportunity for further adhesion of tissues. A culture from the cyst grew *Staphyloccocus intermedius* and Dakota was placed on 6 weeks of Clavamox.

In July 2017 at the age of four, Dakota returned to MSU-CVM for a 4 day history of constipation, lethargy, and decreased appetite. Bloodwork revealed no abnormalities and no evidence of intestinal obstruction was seen with barium contrast. However, multiple smoothly-marginated hypoechoic ovoid masses were seen on ultrasound. The largest of the masses measured 4cm x 4cm. Additional areas of corrugation of the small intestines was seen in comparison to prior ultrasound studies. These areas of corrugation and nodulation were consistent complications of her chronic disease as the proliferation of mature collagenous tissue and their resulting adhesions tend to cause irregularities in overall tissue architecture. At this point, it was assumed that more nodules would appear and intestinal obstruction may become a complication in the future. Regularly scheduled abdominal ultrasound and barium studies would best monitor the progression.

Returning to her final presentation on May of 2018, Dakota was bright, alert, and responsive. She weighed 36.3 kg. She had a temperature of 101.5 degrees, a pulse rate of 60 beats per minute, and a respiratory rate of 36 breaths per minute. She had a body condition score of 5/9. There were normal bronchovesicular sounds in all lung fields. There were no murmurs or arrhythmias on cardiac auscultation. The abdomen appeared slightly distended, and while palpation did not elicit a painful response, Dakota's abdomen was tensed and individual organs could not be appreciated. The sclera of the eyes were slightly icteric, as were the pinnae of the ears. On repeated abdominal palpation, the cranial border of the abdominal wall felt unusually tensed. The remainder of the physical exam on presentation was within normal limits.

Diagnostic Approach/Considerations:

Tests for assessing the status of the hepatobiliary system include serum enzyme activities. Tests that assess the functionality of the hepatobiliary system include measuring serum albumin, serum urea nitrogen, and serum bilirubin concentrations, as well as the cholesterol, glucose, ammonia and/or bile acids concentrations. On the day of presentation, blood was drawn to recheck liver values and confirmed markedly increased ALT at 2385 U/L, a markedly increased ALP at 2860 U/L, and an increased total bilirubin at 5.9 mg/dL. An ammonia tolerance test indicated adequate liver function, and coagulation times were within reference range. The owners assured there was no possibility of Dakota consuming known hepatotoxins in her environment, which included xylitol and certain medications. Another rule out for this presentation included *Leptospirosis*, however testing was not pursued due to vaccination history. *Bartonella* was noted as another cause of this presentation. Findings on abdominal ultrasound were unchanged from previous visits and consistent with her chronic condition. The liver did, however, appear normal on both ultrasound and radiographic imaging. Liver fine needle aspirates taken during abdominal ultrasound were non-diagnostic. Dakota was admitted and treated as an acute hepatopathy of unknown origin. She was treated symptomatically with IV fluids, as well as metoclopramide, Unaysn, enrofloxacin, Entyce, Cerenia, and pantoprazole.

The following day, Ursodiol, Denamarin and N-acetylcysteine were added to her treatments. Dakota was maintained on supportive treatment over the weekend, during which time her appetite remained inconsistent. On the morning of the second day of hospitalization, a repeat liver panel revealed improved, yet still increased ALT and ALP values at 1438 U/L and 1795 U/L respectively. BUN was decreased at 5 mg/dL, albumin was decreased at 2.4 g/dL, and total bilirubin increased slightly more at 6.7 mg/dL. Dakota continued to be disinterested in most food, and would eat only if hand-fed. Entyce was added to her treatment regimen. Her presenting level of icterus remained.

Dakota became progressively more lethargic and icteric by day 4 of hospitalization. She was scheduled to undergo liver biopsy, but her rapid decline prevented such a diagnostic. Bruising and edema of her extremities developed overnight. Her respiratory rate had increased markedly by that morning, and she became progressively more depressed. Abdominal fluid was found on FAST scan, and thoracic radiographs revealed pleural effusion.

Blood was taken again for a liver panel. An overall downward trend of cholesterol and total protein levels was noted. BUN and albumin levels continued to decline at 6 mg/dL and 2.4 g/dL respectively. Total bilirubin, ALT and ALP were improved at 4.5 mg/dL, 872 U/L, and 1595 U/L respectively. This was an anticipated trend since fewer and fewer living and secreting hepatocytes exist to provide these enzymes to the serum in an ongoing manner. By the time of the last blood draw, clotting times were prolonged with a PT of 18.1 seconds and a PTT of 23.9 seconds. Extremity edema as well as whole body bruising was worsening by the hour. Worsening liver function was suspected at this point and this along with her clinical deterioration was discussed with Dakota's owners earlier that day. Dakota was humanely euthanized that evening to prevent suffering.

Pathophysiology:

Hepatocytes are histologically arranged into 3 zones following the flow of blood through the liver. Cells found in the area of highest oxygen concentration due to blood exposure are within zone 1. Zone 2 contains hepatocytes between zone 1 and the area furthest from vascular flow, zone 3. Zone 3 hepatocytes carry the lowest respective oxygen concentration, and thus are considerably more susceptible to hypoxic injury, as well as toxic metabolities of the cytochrome P450 system. Because the liver has a vast reserve, manifestation of hepatic disease are often inapparent until 70% of functional hepatocytes are lost. [9] Inflammation and necrosis can lead to rapid systemic deterioration beyond this point.

As mentioned, increases in liver-specific serum enzymes, which are normally found in the hepatocyte cytosol, reflect structural and/or functional cell injury and assess the status of the hepatobiliary system. Alanine transaminase, or ALT, is the most useful liver-specific enzyme indicating hepatocellular injury in dogs and cats. However, ALT is not found to be increased unless there is actively ongoing injury occurring within a certain timeframe, as the serum half-life is 59 hours in dogs and less than 24 hours in cats. [3] Additionally, liver enzyme activity may decrease over time in the end-stages of liver failure, as fewer and fewer living, secreting hepatic cells remain. Aspartate transaminase, or AST, while found in hepatocytes and hepatic mitochondria, is not organ-specific. Instead, it is found in the greatest concentration in skeletal muscles, and may also be found in cardiac tissue. AST increases solely due to muscle tissue damage, are generally accompanied by an increase in creatine kinase. Generally though, the greatness of ALT and AST serum rise approximates the extent of hepatocellular

injury, but the same cannot speak to the reversibility of damage. Other serum enzymes that can increase in liver injury are the cholestatic inducible enzymes, alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT). Cholestasis is the strongest stimulus for these increases, where dead or dying hepatocytes begin to block bile flow. Additional and secondary liver damage can occur here, as bile acids act as emulsifying agents on neighboring liver tissue.

The liver acts as the major gateway between the GI tract and systemic circulation, and in maintaining balance between the two lies the greatest concentration of fixed macrophages in the body. These Kuppfer cells trigger massive release of cytokines during liver necrosis, leading to a systemic inflammatory state, which can end in hypoperfusion of tissues and multi-organ system failure.

Hypoglycemia is a frequent complication of acute liver failure. Weakened gluconeogenesis and decreased insulin absorption by impaired hepatocytes is the driver behind this abnormality, again furthering the progression of disease. The maintenance of blood sugar for energy production is of key importance, considering the array of metabolic disturbances and stressors taking place in liver failure. Hypoglycemia only acts to exacerbate problems in an already taxed body.

Coagulopathy is a hallmark in acute liver injury, given that all clotting factors are made in the liver, except for factor VIII and von Willebrand factor. The driving force behind abnormal clotting tests are the decreased production of factors II, V, VII, IX, and X. [6] Bruising will appear as these factors continue to decline. However, coagulopathies are unusual in cats and dogs with most hepatobiliary disease states, apart from those in fulminant liver failure or DIC. [8]

The detoxification of ammonia products from the intestines and production of water-soluble urea to do so only takes place in the liver. Those in liver failure or partakers of a low protein diet will have decreased levels of serum urea nitrogen. Ammonia is a powerful circulating neurotoxin. When combined with the inflammatory mediators released in liver failure or necrosis, the two act to both alter cerebral blood flow and compromise blood-brain barrier permeability. The consequence is encephalopathy via astrocyte swelling and cerebral edema. Hepatic encephalopathy can vary in its clinical presentation from drowsiness to seizing to coma.

Because fibrinogenesis and fibrinolysis are imbalanced in sclerosing encapsulating peritonitis, it is not a stretch to associate the condition with oncoming liver disease/dysfunction. In one histological study of a dog with sclerosing encapsulating peritonitis, the liver was found to be thickened “by mature collagenous connective tissue

admixed with immature collagenous connective tissue," as well as fibrotic central veins. [3] Cirrhosis, or severe fibrotic change to the liver, is well known to cause substantial morbidity and mortality in both humans and animals.

Though the exact cause of sclerosing encapsulating peritonitis remains unknown, inflammatory processes do play a role. Inflammatory markers have been shown in encapsulating peritonitis to increase the production of extracellular matrix components and fibrinogenesis, resulting in fibrocollagenous overgrowth, particularly of the small intestines and abdominal cavity. [1] While fibrosis generally occurs as a reparative response to damage, having a disease that favors the process of fibrin deposition in normal tissues may predispose those to complications like liver disease. Though Dakota's liver FNA was non-diagnostic, if one considers her chronic disease state in this light, it begs the possibility of acute on chronic liver failure vs simply acute liver failure. A period of more than a year spanned between Dakota's final presentations, and although liver values were normal at one time, that period allows enough time for significant hepatic changes to develop.

Treatment and Management:

While in the hospital, Dakota received metoclopramide for nausea and potential GI stasis, N-acetylcysteine for liver support, Denamarin as an antioxidant, Ursodiol to aid cholangitis, Cerenia for nausea, hydromorphone for pain management, as well as Unasyn and enrofloxacin to provide four-quadrant antimicrobial coverage. Growing evidence supports the use of N-acetylcysteine for not only paracetamol-induced acute liver failure, but in most all etiologic causes of acute liver failure. [8] It is commonly used in acetaminophen toxicity, as it is a precursor for the production of the master detoxifier, glutathione. NAC was utilized in Dakota's case with the understanding that any aid to free radical scavenging and liver detoxification should be provided. Although encephalopathy did not manifest in Dakota's case, it has been suggested that NAC may reduce cerebral edema by increasing cerebral blood flow. [8]

As mentioned, the liver is a gateway between the microbially diverse intestinal system and the systemic circulation. When compromised, the use of broad-spectrum antibiotics becomes paramount. In one retrospective study of acute liver failure in dogs, 47% suffered hepatic necrosis, which provides a breeding ground for microbes. [3] Once enough damage is made to the liver, regardless of the degree of necrosis present, good medicine practices should include antibiotics that cover aerobic and anaerobic microbes. Unasyn provides coverage for gram negative

and positives, those that are not beta-lactamase producing strains, *Enterobacteriaceae*, and some anaerobic microbes. Enrofloxacin was incorporated to provide coverage of ampicillin-resistant microbes. Together, they can empirically treat Leptospirosis infection, as it can sometimes lead to hepatic failure.

Fluid therapy was initiated to address dehydration from vomiting. Gastrointestinal protectants, such as metoclopramide and pantoprazole were instituted to address both nausea and the harmful effects of liver failure. When hepatic function is reduced, an increase in bile acids and consequential increase in gastrin production occurs, potentially leading to gastroduodenal ulceration. Additionally, when albumin is reduced, gastric mucosal turnover is reduced, altering the mucosal barrier, which also predisposes to ulceration.

While blood products rich in platelets and coagulation factors, such as plasma, are indicated in the treatment of liver failure, it was not utilized in Dakota's case because clotting times remained normal until the rapid onset of end-stage disease. However, coagulation tests often do not become abnormal until a large percentage of clotting factors are absent. Dakota's prolonged clotting times were taken into account when discussing prognosis.

Case Outcome:

Dakota was humanely euthanized and was cremated. A necropsy was not performed in alignment with owner's wishes, and the cause of acute liver failure remains unknown. In a recent retrospective study, the most common etiology of acute liver failure in 49 dogs was neoplasia. [3] *Leptospirosis* remains another cause of acute liver failure presentation, but tends to resolve with appropriate therapy. A decline to necropsy prevents histologic examination of the liver, and it remains entirely possible that what may have been seen is extensive hepatic fibrosis. If seen, Dakota's case could be another example associating acute liver failure with sclerosing encapsulating peritonitis.