Tyler's Anomaly(ies)

Gunnar R. Dunnam

Mississippi State University

College of Veterinary Medicine

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Advisor: Betsy Swanson, DVM, MS, DACVS-SA

Introduction

The portal vascular system functions to drain the venous supply of the stomach, intestines, spleen, and pancreas. With normal anatomy, the portal vein carries blood and catabolic products to the liver for further metabolism, anabolic processes, and detoxification.[3] The liver functions to regulate blood glucose levels by gluconeogenesis and glycolysis. Additionally, it synthesizes a vast array of compounds such as cholesterol, BUN, clotting factors, and albumin.[7] The portal vein supplies approximately 80% of the hepatic blood supply with the remaining 20% coming from the hepatic artery.[3] Anomalous vessels that connect the portal vein to systemic circulation, therefore bypassing the liver, are referred to as portosystemic shunts and impair liver function due to decreased blood flow.[1] This shunting can either be from an acquired portosystemic shunt (APSS) or a congenital portosystemic shunt (CPSS).[4] APSSs result from microscopic embryonic communications that enlarge in response to increased portal pressures and are reported to account for up to 20% of PSSs diagnosed in dogs.[4] APSSs are generally seen in older animals; however, they have been reported in younger individuals. Therefore, age should not be used as a sole criteria for differentiating between APSSs and CPSSs.[4] Usually presenting in younger animals, CPSSs are the most common portosystemic vascular anomaly and are the result of inappropriate vessel development or failure of a normal vessel to close. [3] These shunts can either be classified as intrahepatic or extrahepatic. Intrahepatic shunts usually arise from failure of the ductus venosus to close following birth and are more common in large breed dogs.[3,5] Extrahepatic shunts are more common in small breed dogs and are classified based on their origin and insertion.[3,5] In one study, the prevalence of CPSSs in dogs was 0.18%. This corresponded to 2,400 cases of which Yorkshire Terriers and Miniature Schnauzers contributed 20.1% and 10.2% of the total cases, respectively.[2]

Differential Diagnosis & Diagnostic Approach

Patients who present with the non-specific clinical signs of a PSS should have a CBC and chemistry performed. Blood work should show values suggesting that the liver is not functioning properly due to insufficient blood flow. These abnormalities will usually include hypoglycemia, hypoalbuminemia, hypocholesterolemia, decreased BUN, elevated ALT, and elevated ALP.[1] A typical urinalysis will have a decreased specific gravity due to PU/PD and could contain ammonium biurate crystals. These abnormalities are not specific for a PSS; other differential diagnoses would include hepatic cirrhosis, liver damage (acute or chronic), or chronic low protein diet (malnutrition).

Further work up for a PSS will include liver function testing. A bile acid test can be employed to assess the liver's ability to extract bile acids from portal circulation.[11] This test measures both hepatocyte function and biliary system function. The testing procedure includes taking a fasting blood sample and a 2-hour post-prandial sample. Pre-prandial values >20-50umol/L approach a sensitivity of 100% for liver dysfunction.[1] An ammonia tolerance test (ATT), which tests the hepatocytes ability to clear ammonia, may also be utilized. A fasting ammonia serum sample is obtained and if elevated, the test is finished because additional ammonia can exacerbate clinical signs and lead to severe hepatic encephalopathy.[3] The ammonia tolerance test is more specific for portal vascular anomalies than a bile acid test and basal levels are generally diagnostic.[3]

Imaging can then be used to locate the shunt and determine if it is extrahepatic or intrahepatic. Radiographs are generally not specific and can show microhepatica and bilateral renomegaly. One study found that abdominal ultrasound was 92% sensitive and 98% specific in diagnosing PSSs; however, there are reports of larger variations based off of the

ultrasonographer.[8] Nuclear scintigraphy can also be used to diagnose a shunt. This procedure includes administering the radioisotope technetium pertechnetate (^{99m}Tc pertechnetate) intra-rectally or trans-splenic. A gamma camera is then used to estimate the amount of blood bypassing the liver. This test can diagnose a shunt, but it generally cannot characterize it.[3] Computed tomography (CT) with contrast is considered the gold standard for diagnosis.[3] It is used for diagnosis as well as for surgical planning.

History & Presentation

Tyler is an approximately 5-month-old intact male Dachshund mix that presented to MSU-CVM Small Animal Surgery Service on December 4th, 2019. Tyler was rescued on September 15th, 2019 when he was 10 weeks old. Three days later, he was noted to be acutely lethargic and head pressing. He presented to his local veterinarian where blood work revealed a mild hypoproteinemia, moderate increase in ALP, mild increase in ALT, slightly decreased BUN as well as elevated pre- and post-prandial bile acids. He was started on lactulose at 400 mg/kg and Hill's l/d, at this time, for a suspected portosystemic shunt. On October 22nd, Tyler's bile acids were retested and were elevated both pre- and post-prandial. He was maintained on lactulose and a low protein diet which controlled his clinical signs. On November 6th, he presented to his local veterinarian for suspected aspiration pneumonia where a 2 view thoracic series was performed. This study or report was not provided to MSU-CVM. He was started on Clavamox and his owner noted that he had an acute reaction (vomiting and lethargy); Tyler represented to his veterinarian the following day. The referring veterinarian noted that Tyler had approximately 20 ant bites at the time of presentation; Clavamox was then discontinued, and he was given a single dose of Convenia. On November 12th, Tyler was started on levetiracetam

(Keppra) at 24 mg/kg PO q12. Tyler was up to date on vaccinations, but he was not currently on flea, tick, or heart worm preventative.

On presentation, Tyler was quiet, dull, and responsive. Upon thoracic auscultation, no crackles, wheezes, murmurs, or arrythmias were noted. His temperature, pulse, and respiration were within normal limits and he weighed 3.4 kg. He was tense and non-painful upon abdominal palpation. A brief neurologic exam was unremarkable with a slight decreased menace. His tail was noted to be kinked (historic break) at the junction between the middle and distal ⅓. A rectal was not performed. Two testicles were palpated within the scrotum. The rest of the exam was unremarkable.

Based on Tyler's signalment, history, and previous blood work, a portosystemic shunt was suspected (and the reason for referral). A CBC revealed a microcytic normochromic anemia (PCV 30%) and a moderate leukocytosis (29.91 10^3/ul) characterized by a neutrophilia (18554/ul), lymphocytosis (6879/ul), and eosinophilia (3589/ul). A chemistry panel revealed a moderate hypoglycemia (67 mg/dl), mildly decreased BUN (4), moderately elevated ALT and ALP (424 and 355 U/L, respectively), panhypoproteinemia characterized by a marked hypoalbuminemia (1.3 g/dl) and moderate hypoglobulinemia (1.8 g/dl), a moderate hypocholesterolemia (66 mg/dl), and a mild hyperphosphatemia (7.3 mg/dl). Tyler was then sedated for an abdominal computed tomography with contrast. This study revealed a single, extrahepatic portocaval shunt, microhepatica, an ill-defined portal vein cranial to shunt origin, a large amount of peritoneal effusion, and a diffusely thickened pancreas with fluid attenuating material and heterogenous contrast-enhancing vessels throughout it.[12] In the stomach, there were multiple mineral and metal attenuating structures. The lungs revealed a patchy alveolar pulmonary pattern in the ventral aspect of the cranial subsegment of the left cranial lung lobe and

right middle lung lobe.[12] The following morning on December 5th, Tyler was fed approximately 2 tablespoons of Hill's l/d for his hypoglycemia and was later sedated for thoracic radiographs which revealed an alveolar pulmonary pattern with major consideration given to atelectasis.[12]

Treatment and Management Options

Depending on the type of shunt present, both medical management and surgical correction can be used and are often used together. The main goal while managing an acute hepatic encephalopathy (HE) patient is to correct electrolyte disturbances, maintain blood glucose levels, and decrease the ammonia levels via warm water or lactulose (30%) enemas, a protein-restricted diet, oral lactulose, and antibiotics such as metronidazole, ampicillin, and neomycin.[3] These medications stabilize the patient by decreasing the overall amount of ammonia in systemic circulation. Rectal enemas and antibiotics decrease bacterial loads within the colon thus reducing ammonia production/absorption. Lactulose acts to lower the colonic pH which traps ammonium as well as to increase intestinal transit time. Once stabilized, the patient can be medically managed on a low protein diet, lactulose, +/- antibiotics and seizure metaphylaxis until they are stable enough for surgery.[3] Medical management alone should not be considered as the sole treatment unless the client refuses surgery, or the vascular anomaly is inoperable as with primary hypoplasia of the portal vein (PHPV), multiple acquired shunts, and certain intrahepatic shunts.[3] One study showed that medical management alone resulted in over half of the dogs being euthanized with a median survival time (MST) of 9.9 months. Approximately ⅓ of the dogs had a MST of 56.9 months with a range of 5 months to >7 years.[3]

Surgery is warranted if owner finances and shunt type allows. The options for surgical correction include an exploratory laparotomy where the shunt is identified and isolated. Then, one of three main techniques are used to occlude the shunt. Direct silk suture ligation is one

option. This option is less frequently used due to the increased risk for portal hypertension and hepatic encephalopathy.[6] An ameroid constrictor and cellophane band are the other two surgical options. These options cause gradual occlusion of the shunt by causing a fibrosis reaction.[3] Another less common option is a hydraulic occluder which has a cuff that is placed around the shunt and an external port which is maintained to allow for sterile water injection every 2 weeks until the shunt is gradually occluded over 6-8 weeks.[3] Interventional radiology can also be employed to attenuate intrahepatic shunts (and less commonly extrahepatic) that may not be correctable via other surgical methods.[3] This method uses fluoroscopy to thread a guidewire from the jugular vein (right is preferred) to the mouth of the shunt where a stent is placed followed by thrombogenic coils.[13] The main post-operative complications from shunt attenuation are portal hypertension (PH), seizures, and coagulopathies.[10]

A brief, unofficial, single abdominal organ ultrasound was performed (no report) to assess the pancreas before surgery. Tyler was then anesthetized, and an approximate 8cm ventral midline incision was made. A full abdominal exploratory was then performed. The mesoduodenum was retracted medially, and the caudal vena cava was located. At the level of the epiploic foramen, a vessel was coming in at approximately a 90-degree angle and turbulent blood flow was noted within the caudal vena cava. Blunt dissection was used to isolate the anomalous vessel and two nylon sutures were passed to temporarily occlude the shunt to assess for gross portal hypertension and allow for manipulation of the vessel. An ameroid constrictor was then placed on the vessel. A gastrotomy was performed where a large amount of concreted food was removed along with a foreign object with a metal spring. A routine pre-scrotal neuter was then performed. Tyler recovered well; however, dexmedetomidine was flushed through his arterial catheter by mistake. He was maintained on remifentanil 1.5 mcg/kg/hr, Keppra 24 mg/kg PO

q12, lactulose 400 mg/kg PO q12, and trazodone 3.5 mg/kg PO q8. His glucose was monitored, and he had an episode of hypoglycemia at midnight with a BG of 65 mg/dl. 2.5% dextrose in lactated ringer's solution was then added to his IV fluids. The following day he was noted to regurgitate. The 2.5% dextrose CRI and remifentanil were discontinued, and he was started on Tylenol 3 2 mg/kg PO q8, sucralfate 142 mg/kg PO q12, pantoprazole 0.5 mg/kg IV q24, and maropitant 1 mg/kg IV q24. He was otherwise maintained on Keppra 24 mg/kg PO q12, lactulose 400 mg/kg PO q12. He ate 4 times throughout the day (treatments sheet said ⅓ cup per feeding, but one feeding it was noted that he only ate 2 tablespoons). At approximately 5am the next morning, it was noticed that Tyler's abdomen was distended, and he was uncomfortable. An aFAST was performed which showed his abdomen full of air and hyperechoic material (suspected to be his stomach). Abdominal radiographs were then performed, and Tyler was diagnosed with food bloat. He was maintained on all prior medications, and pantoprazole was exchanged for omeprazole at 1mg/kg PO q12. A plasmalyte CRI was added, and food was withheld. 2 mls of Karo syrup were given by mouth every 4 hours to avoid hypoglycemia, and glucose readings were taken every 12 hours but staggered from syrup administration. His walks were increased from every 8 to every 6 hours. The following day (December 5th, 3 days post-operative), Tyler was still uncomfortable and had signs of food bloat both externally and on aFAST. His feces was soft with frank blood at the beginning of defecation. Tyler was swapped to a strict NPO status by removing water and changing from oral omeprazole back to injectable pantoprazole 1 mg/kg IV q12. In addition, Tyler was walked for longer durations and metoclopramide was added at 1.5 mg/kg/day as a CRI. Day 4 post procedure, abdominal radiographs showed resolution of food bloat but a pendulous abdomen. Tyler was discharged with kennel confinement, incision care, monitoring, and feeding instructions. He was discharged

with Tylenol 3 2 mg/kg PO q8 for 6 days, sucralfate 142 mg/kg PO q12 for 7 days, and omeprazole 1 mg/kg PO q12 for 7 days. He was also continued on lactulose and Keppra at the original dose and frequency for 4-6 weeks to give the shunt enough time to occlude. Follow up care included an incision check 10-12 days from discharge and pre- and post-prandial bile acids to be performed in 6-8 weeks.

Pathophysiology

It is suspected that Tyler developed portal hypertension (PH) due to clot formation following the placement of the ameroid constrictor. Portal hypertension can be classified as either prehepatic, hepatic, or posthepatic and is the result of any increase in pressure of the portal system.[9] Prehepatic can be due to increased pressure on the extrahepatic portal vein due to a luminal or extraluminal lesion such as with portal vein hypoplasia, fibrosis, thrombosis, or neoplasia. Other causes of prehepatic PH include hepatic arteriovenous fistulas, complication of CPSS attenuation, and trematode infestation.[9] Hepatic PH is due to direct changes of the liver architecture and can be classified as presinusoidal, sinusoidal, or post sinusoidal disorders that inhibit blood flow such as with primary hypoplasia of the portal vein (PHPV) and fibrotic disorders. Post-hepatic PH is associated with disorders of the right side of the heart, larger hepatic veins, or caudal vena cava.[9] Regardless of the classification of the PH, it can lead to venous congestion of the organs that drain into the portal vein. This results in clinical signs of post-operative portal hypertension which is characterized by organ edema and ascites formation that leads to hemodynamic instability, abdominal pain/distention, melena, diarrhea, and hypovolemia.[10] Intraoperative signs of portal hypertension include hypermotility of the intestines and engorgement of mesenteric vessels after acute ligation of the shunt. This can be assessed before shunt attenuation by temporarily manually occluding the shunt.

Case outcome

The day after discharge from MSU-CVM, Tyler presented to his rDVM for discomfort, abdominal distention, coughing, and diarrhea. A SNAP cPL was normal. Chemistry revealed a persistent marked hypoalbuminemia of 1.4 g/dL and ALT mildly elevated at 110 U/L. CBC showed a continued severe microcytic anemia (HCT 21.4%) and a leukocytosis characterized by a moderate neutrophilia (31.87 K/uL), mild monocytosis (5 K/uL), and mild eosinophilia (2.22 K/uL). An abdominocentesis was performed draining an unknown amount of fluid that was noted to return "quickly." This fluid was determined to be a pure transudate with a total protein of 0.0 mg/dL. He presented to MSU-CVM 3 days later (4 days from previous discharge). Tyler presented with a major complaint of ascites and a referral for an abdominal ultrasound. Physical exam showed a largely distended abdomen with an appreciated fluid wave; the remainder of the exam was within normal limits. At this visit, a blood chemistry revealed mild hyponatremia (135.3 mmol/L), mildly increased ALT (108 U/L), mildly increased ALP (276 U/L), moderate hypoalbuminemia (1.8 g/dl), and mild hyperphosphatemia (6.2 mg/dl). CBC revealed an improving microcytic anemia with a PCV of 28%, mild neutrophilia (16369/ul), and mild monocytosis (1991/ul). Ultrasound findings revealed gallbladder debris, a large amount of free fluid within the abdomen, bilateral nephrocalcinosis, and normal portal vein velocity.[12] The pancreas had a similar lobular pattern as previously described on the abdominal CT.

Dr. Karen Tobias (UTCVM) was consulted on this case. It was recommended that the rDVM start spironolactone. The ascites resolved within 2 days of initiating spironolactone. A CBC, chemistry, and bile acids were obtained at Tyler's rDVM at his 8 week recheck. Tyler was clinically normal and had gained weight. His pre-prandial bile acids were mildly elevated at 37 (RR: 0-14.9 umol/L) and post-prandial bile acids were severely elevated at 235.5 umol/L (RR: 0-

29.9ummol/L). Blood work at this time revealed that Tyler had a mild microcytic hypochromic anemia (HCT 34%), mild hyperphosphatemia (8.1mg/dL), mild hypocholesterolemia (107 mg/dL), and panhypoproteinemia with a mild hypoalbuminemia (2.2 g/dL) and mild hypoglobulinemia (1.9 g/dL). His liver values remained mildly elevated with an ALT of 167 U/L and ALP of 212 U/L.

Discussion

In Tyler's case, his abnormal post-operative complications could be attributed to portal hypertension. It was likely due to a clot formation at the ameroid constrictor which inadvertently occluded the portocaval shunt immediately rather than gradually over time. This resulted in increased pressure in the portal vein which led to increased hydrostatic pressure. Couple this increased hydrostatic pressure with the already decreased oncotic pressure (hypoalbuminemia) and ascites formation occurred postoperatively. This is also the reason it returned so quickly after the rDVM drained it. The food bloat could be due to the congestion of the stomach from PH or direct ileus from the gastrotomy. The bloody diarrhea could be an incidental enteritis from surgery or food bloat but could also be caused by intestinal hypermotility from the PH and variceal bleeding. His hypoglycemia was expected and occurs in 44% of dogs after EHPSS attenuation.[3] There was no confirmation of portal hypertension as this is usually an invasive procedure that is done during surgery or under anesthesia through direct catheterization of the portal vein or a tributary. The portal vein velocity was reported to be within normal limits at the organ recheck ultrasound. However, Ohm's law defines pressure as velocity multiplied by resistance.[9]

What cannot be explained by the suspected post-operative PH is the degree of ascites prior to surgery, presence of a large amount of food during his gastrotomy, and pancreatic edema

prior to surgery. These findings suggest that Tyler had portal hypertension prior to surgery caused by an underlying condition such as PHPV (previously known as microvascular dysplasia) in addition to the extrahepatic portosystemic shunt. Intraoperative liver samples were not taken during the procedure for histopathology because he was doing poorly under anesthesia. Therefore, hepatopathies cannot be ruled out. Regardless of the cause of the complications, it would not change the current treatment plan that he was on, so symptomatic care and medical management were continued instead of further diagnostics. This case was left with a working diagnosis of a prematurely attenuated extrahepatic portocaval shunt resulting in exacerbation of portal hypertension with future multiple acquired shunts likely, and the possibility of primary hypoplasia of the portal vein.

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