Enzymes gone AWOL

Canine Exocrine Pancreatic Insufficiency

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Introduction

Exocrine pancreatic insufficiency (EPI) is a disorder characterized by deficient secretion and release of pancreatic digestive enzymes by the pancreatic acinar cells resulting in maldigestion. [5] This maldigestion results in the clinical signs associated with EPI including frequent and foul-smelling yellow feces, weight loss, polyphagia, and the malabsorption can result in coprophagia.[5]

Diagnosis of EPI is made with a combination of clinical signs and specific testing most frequently with the cTLI test.[5] A common signalment includes young dogs and breeds such as the German Shepherd, Cavalier King Charles Spaniel, Chows, Rough-Coated Collies, and West Highland White Terriers.[3] Signalment paired with clinical signs is enough evidence to warrant a cTLI test which is diagnostic for EPI when < 2.5 ug/L. Although there is no treatment to reverse the already sustained damage to the exocrine pancreas, supplementation is a viable and long-lasting therapy.

Treatment involves supplementation of digestive pancreatic enzymes through a powder mixed with food.[5] Studies have compared varies enzyme supplementation such as powder, granules, capsules, enteric coated tablets, and finely chopped raw pig pancreas, and the powder supplementation achieved one of the highest enzymatic activity in the small intestine.[1] Prognosis is mostly favorable with response to initial therapy; however, unfortunately some patients do not respond to supplemental therapy.[6]

History and Presentation

Abel is a 4.5 year old male neutered pit mix that presented to MSU-CVM Emergency Service on 12/23/2019 for chronic weight loss and diarrhea. Abel had a 4-5 month history of weight loss, but more recently he was boarded for 4 days with his primary care veterinarian and

had lost 8 pounds. He had ongoing diarrhea which had become more urgent within the month prior to presentation and his appetite was increased. He and his owner were living in Florida at the time of presentation, but are originally from Starkville, MS and had returned home for the holidays. Back in Florida Abel has been evaluated by multiple different veterinarians in search of a diagnosis and they have tried many different medications including allergy drops which have not helped. Abel was then referred to MSU-CVM by Dr. Westbrook in Starkville for further work-up.

Upon presentation to the MSU-CVM Emergency Service on 12/23/19, Abel was quiet, alert, and responsive. He weighed 13.3 kg and had a poor BCS of 3/9. His vital parameters were within normal limits: temperature 99.5 F, heart rate of 127 beats per minute, and 32 breaths per minute. He was estimated to be ~7% dehydrated with tacky, pale-pink mucous membranes, a delayed skin tent, and a CRT of 2 seconds. His third eyelids were pronounced bilaterally. His skin coat was dull, uneven, and flaky. His abdomen was soft and non-painful on palpation. There were no murmurs, arrhythmias, crackles, or wheezes noted on cardiothoracic auscultation. Prescapular and popliteal lymph nodes were mildly enlarged. Upon rectal exam, no abnormalities were noted. A brief neurological exam was unremarkable. Triage examination revealed that he was adequately oxygenated and normotensive (120/60 (81), 113/60 (76), 107/69 (76)) with a normal sinus rhythm. No free fluid was noted on aFAST or tFAST. His PCV was 33% and TP was 5.5 mg/dL.

Diagnostic Approach

The history, signalment, and clinical signs should be the first step in indicating an idea of EPI. History and clinical signs of chronic weight loss with a normal to increased appetite, increased frequency and volume of defecation, and steatorrhea should raise suspicion of EPI.[5]

German Shepherd Dogs, Rough-Coated collie, Cavalier King Charles Spaniel, West Highland White Terriers, and Chow Chows who are between 3-5 years old are predisposed for EPI.[3] A CBC and chemistry should be performed to screen for systemic organ health, but these results are often unremarkable in EPI.[1,5] If chronic pancreatitis is present additional clinical signs and clinicopathologic abnormalities may be present[5] For a definitive diagnosis of canine EPI, the cTLI test is recommended. In canine EPI cTLI is low; however, false increases in TLI may occur in patients with concurrent renal disease or pancreatic inflammation.[7]

The canine serum trypsin-like immunoreactivity (cTLI) is considered the most sensitive and specific test for diagnosing EPI.[3] The sensitivity and specificity for a low cTLI concentration for EPI is close to 100%.[6] The cTLI test measures canine specific trypsinogen and trypsin-like immunoreactivity in the serum.[4,7] In a physiologically normal pancreas, trypsinogen is synthesized in enough quantity from turnover of pancreatic acinar cells that some is leaked into the blood.[4,7] A pancreas with enough pancreatic acinar damage to cause EPI would have a severely decreased amount of pancreatic acinar cell turnover resulting in miniscule amounts of trypsinogen leakage into the blood.[7] The cTLI test is considered diagnostic for EPI when < 2.5 ug/L.[1,3,4,6] Normal cTLI values are above 5.7 ug/L, and results should be interpreted with caution if they are between 2.5 ug/L and 5.7 ug/L,.[4,7] If results are between 5.7 ug/L and 2.5 ug/L a cTLI should be repeated in 1-3 months.[4]

In one study where 44 dogs tested for EPI resulted in the gray zone (cTLI between 2.5ug/L and 5.7 ug/L), a second cTLI sample was taken 1-3 months later. The results were as follows: 20 dogs had a normal second sample, 13 stayed in the gray zone, and 11 became diagnostic for EPI.[7] The 13 dogs which remained in the gray zone underwent surgery for a biopsy and histopathology of the pancreas. All 13 dogs had a significant loss of exocrine

pancreatic tissue, but 8 dogs showed no GI signs and 5 dogs had irregular GI signs inconsistent of EPI.[6] This study proves the significance of retesting a cTLI in dogs that fall in the gray zone due to the chance of developing signs of EPI in the future.[7]

Another test to consider for EPI is the fecal elastase-1 measurement. Canine fecal pancreatic elastase-1 is a protease specific to the pancreas that is not degraded through intestinal transit.[7] Studies have shown that measuring this enzyme is only 56% specific for diagnosis of EPI.[7] The sensitivity of this test is 100% which would make it an ideal screening test for EPI, but as cTLI is both highly sensitive and specific it is commonly recommended as both a screening and confirmatory test.[7]

In Abel's case, he fit the history of EPI with chronic weight loss and maldigestive diarrhea, but he also had other problems such as anemia and dehydration. A CBC, chemistry, urinalysis, and baseline cortisol were run to assess systemic organ health and screen for Addison's disease. CBC revealed anemia (PCV 26%) and chemistry showed hypokalemia (3.4 mmol/L), hypoproteinemia (4.8 g/dl), hypoalbuminemia (2.1 g/dl), hypocalcemia (8.5 mg/dl), and hypocholesterolemia (107 mg/dl). Baseline cortisol was not diagnostic for Addison's with a cortisol of 4.3 ug/dl, and urinalysis was unremarkable. A GI panel send out test to Texas A&M was submitted, but results would not come back for several days. The results of the GI panel were a low normal cobalamin (279 ng/L) and low cTLI (2.4 ug/L) which was diagnostic for EPI. Since we did not have the results of the GI panel, further diagnostics were performed to investigate the electrolyte abnormalities and protein loss. A further potential option would have been a trial with pancreatic enzymes.

Additional diagnostics for Abel consisted of abdominal and chest radiographs, abdominal ultrasound, gastroduodenoscopy, and colonoscopy. These diagnostics were pursued due to the

suspicion of an inflammatory, infectious, or neoplastic process in the GI tract. Chest and abdominal radiographs were unremarkable. On abdominal ultrasound, enlarged abdominal lymph nodes and multiple hypoechoic nodules throughout the splenic parenchyma were observed. Ultrasound guided fine needle aspirates of the abdominal lymph nodes and spleen were taken, but cytology of the lymph nodes and spleen were unremarkable and non-diagnostic. Based on differentials of lymphangiectasia and inflammatory bowel disease (IBD), gastroduodenoscopy and colonoscopy was pursued. Gastroduodenoscopy revealed a grossly normal esophagus and stomach, but the duodenum had a diffuse, cobblestone appearance. The duodenal mucosa was highly friable with "snow plowing" noted. The rectum and colon appeared grossly normal. The ileum appeared as the duodenum did (highly friable, moon-scape appearance) along with multiple areas of white pinpoint spots suspected to be dilated lacteals. A moderate amount of green feces made the colon and ileum difficult to evaluate. Pinch biopsies were taken of the stomach, duodenum, ileum, and colon. The biopsy results were conclusive of gastroenteritis extending from the stomach to the colon; however, the changes were generally mild except for the severely affected duodenum. The inflammation contained neutrophils which suggested a bacterial component. The lymphangitis present in the lacteals of the duodenum showed plump, reactive endothelium with occasional neutrophils. This was not definitive for lymphangiectasia but could be causing similar clinical consequences such as a protein losing enteropathy.

Pathophysiology

EPI is caused by a lack of synthesis and secretion of digestive pancreatic enzymes from the exocrine pancreas. Chronic diseases such as pancreatic acinar atrophy (PAA), chronic pancreatitis, and pancreatic neoplasia are the most common causes of EPI. Pancreatic acinar

atrophy is by far the most common cause of EPI with chronic pancreatitis being the second most common cause. Pancreatic neoplasia is a rare cause of EPI. Signs of maldigestion are not observed until 90% exocrine pancreatic loss due to the enormous reserve secretory capacity of the exocrine pancreas.[1,2,5]

PAA is targeted destruction of the pancreatic acinar cells depleting the secretory capacity of the exocrine pancreas. Although the exocrine function is ultimately lost, the endocrine function of the pancreas is maintained. Initially, PAA was thought to be a hypoplastic disease due to the typical young age in which EPI developed; however, studies have shown that PAA is a progressive disease. This was proven by following a German Shepherd puppy whose parents had PAA. This puppy developed PAA later in life, but the pancreas was morphologically normal based on histopathology results at a young age. Experimental studies have also shown that PAA can be caused by ischemia, pancreatic duct obstruction, toxicity, and nutritional deficiencies or imbalances, but no evidence has supported these factors in a dog with naturally occurring PAA.[1,2]

Immunohistochemical analysis of PAA has shown an increased population of T-Lymphocytes (CD4+ and CD8+ in equal numbers) in areas of acinar destruction. Other studies have also shown that the humoral immune system is activated in PAA. Therefore, to describe the pathologic findings associated with PAA, it has been termed “autoimmune mediated atrophic lymphocytic pancreatitis”.[1,2] Progression of subclinical to clinical PAA is very unpredictable, and the factors involved with progression of disease is unknown. Factors proposed to influence disease progression include environmental factors such as housing, training, stress, and viruses, but there have been no studies confirming this theory.[1,2]

Chronic pancreatitis is an uncommon cause of EPI, and it undergoes a different pathophysiology of PAA. Chronic pancreatitis causes a progressive destruction of the exocrine and endocrine pancreas; whereas PAA only targets destruction of the exocrine pancreas. Clinical signs which follow chronic pancreatitis are usually associated with those of diabetes mellitus instead of EPI. Clinical signs of EPI often occur after signs of diabetes mellitus.[1,2]

Treatment and Management

The mainstay of therapy for EPI is supplementing the pancreatic digestive enzymes orally.[5] Currently one of the main problems in supplementing pancreatic enzymes is achieving an effective concentration in the small intestine. Most of the pancreatic enzymes are acid labile causing a significant loss of enzymes in the stomach. Companies manufacturing pancreatic enzymes have implemented enteric coating on the enzymes, but achieving a proper concentration of digestive enzymes in the small intestine is still lacking.[1]

The recommended guidelines for pancreatic enzyme supplementation is porcine or bovine pancreatic enzymes mixed with a maintenance diet. The dose is initially 1 tsp/10 kg body weight mixed in with each meal, but this dose can be reduced as clinical signs resolve. Lifelong enzyme supplementation is necessary. If the patient is also cobalamin deficient, cobalamin by subcutaneous injection should be administered. Depending on the dog's size, dosing ranges from 250 to 1200 mcg per injection. These injections are initially given weekly for up to 6 weeks, and then moved to monthly injections with a recheck of cobalamin concentration afterwards. Depending on each dog, some will only need short term supplementation while others need it lifelong.[5]

After Abel's initial presentation on 12/23/19 IV fluids were started to correct the dehydration. On 12/24/19 after initial diagnostic testing of CBC, chemistry, baseline cortisol,

chest radiographs, abdominal radiographs, and abdominal ultrasound, fenbendazole and metronidazole were started due to a possibility of intestinal parasites, and an infectious/inflammatory GI process. He was fed a hydrolyzed diet due to a differential diagnosis of a food responsive enteropathy. The next day, 12/25/19, he continued his medications and was started on a course of enemas in preparation for the upper and lower GI scope. On 12/26/19, the suspicion of an inflammatory canine chronic enteropathy and/or lymphangiectasia was high based on the gross images of the upper and lower GI scope. The last dose of fenbendazole was administered and he was started on prednisone (immunosuppressive dose of 2 mg/kg) and cyclosporine. The GI panel and biopsy results were not back at this time, and he was discharged on 12/27/19. The owners were instructed that the GI panel results and biopsy may result in additional diagnoses and treatments. He was discharged with metronidazole, prednisone, cyclosporine, and Purina HA food with a plan to recheck response to therapy and bloodwork in two weeks.

Case Outcome

Unfortunately, Abel did not do well after he was initially discharged. He had episodes of regurgitation/vomiting after eating, and his diarrhea had worsened to a watery, green/yellow tinge. The next day (12/28/19), he vomited after eating and tried to eat the vomitus, but he then fell over and had a seizure lasting 45-60 seconds according to the owner. The episode was described as falling over suddenly, stiff limbs, and shaking/trembling all over with eyes wide open. He went limp and could not raise his head up. He recovered from this episode, and the owner brought Abel into MSU-Emergency Services on 12/28/19.

Upon presentation, Abel was quiet, dull, alert, and responsive. He weighed 13.5 kg and had a poor BCS of 3/9. He was hypothermic at 96.0 F, heart rate of 80 beats per minute, and

respiratory rate of 20 breaths per minute. He was estimated to be ~10% dehydrated with a prolonged skin tent, sunken eyes, and tacky, pale-pink mucous membranes, and a CRT of ~3 seconds. His third eyelids were pronounced on both eyes. His skin coat was dull with some area of hair loss. His abdomen was soft and mildly painful on palpation. There were no murmurs, arrhythmias, crackles, or wheezes noted on cardiothoracic auscultation. His extremities were cold to the touch. No peripheral lymphadenopathy was noted. Upon rectal exam, no abnormalities were noted although he was leaking watery, mucoid, foul smelling diarrhea. A brief neurological exam was unremarkable.

Triage examination revealed that he was adequately oxygenated and normotensive (119/76 (81), 115/76 (85), 124/83 (96)) with a normal sinus arrhythmia. No free fluid was noted on aFAST or tFAST. He was warmed up with a blanket and Bair-Hugger to 99.8 F. His peripheral blood glucose was 150 mg/dL and a peripheral lactate was 8.9 mg/dL. His PCV and Total Protein was 30% and 6.0 respectively. An iStat revealed a severe metabolic acidosis with respiratory compensation. An IV catheter was placed in his right front leg and a quarter shock dose of Plasmalyte was administered. He was placed in a kennel on twice maintenance fluids and Cerenia was administered IV. Abel was stable throughout the night. He had diarrhea throughout the night hourly, but would drink when offered water.

During hospitalization, a urinalysis was performed and revealed a urine pH of 6. Thoracic radiographs were performed revealing a focal unstructured interstitial pulmonary pattern due to possible atelectasis, pulmonary thromboembolism, or pneumonia. Pleural fissures were also noted which could be due a small volume of pleural effusion or tangential beam artifact. Abel was continued on IV fluids at 70 ml/h (2x maintenance), cerenia (1mg/kg IV Q24), prednisone (2mg/kg PO Q24), cyclosporine (5mg/kg PO Q12), and metronidazole (10 mg/kg PO Q12)

whilst awaiting the results of the GI biopsies. He was also restricted to a novel protein diet in Hill's DD duck. Abel's blood gas abnormalities were sequentially monitored; however, despite clinical improvement blood gas abnormalities persisted, and additional hospitalization was offered but was declined as the owners were returning to Florida. It was strongly recommended that Abel continue seeking medical attention in Florida. On the morning of 12/31/19 the biopsy results from the previous visit returned and revealed plasmacytic, neutrophilic and eosinophilic enterocolitis with lymphangitis. Due to the presence of neutrophilic inflammation and lymphangitis the cyclosporine dose was reduced to q 24 hours and additional testing was submitted, consisting of a fecal culture and a histoplasmosis urine antigen. The fecal culture had moderate growth of gram positive and negative enteric flora, and the histoplasmosis urine antigen test was negative. PCR testing for heterobilharzia was also recommended; however, an adequate sample could not be collected prior to discharge and as such Abel was discharged with a 10-day course of fenbendazole and the owner was instructed to bring in a sample for heterobilharzia testing. A sample for heterobilharzia was later submitted which resulted in a negative test. Given some atypical features of Abel's biopsy results, it was recommended that if Abel did not respond to current therapy full thickness biopsies and fluorescent in situ hybridization should be pursued. Potential causes of the biopsy findings include infectious etiologies and more atypical forms of IBD such as focal intestinal lipogranulomatous lymphangitis. The GI panel results subsequently returned and Abel was started on pancreatic enzymes in addition to cobalamin supplementation.

In conclusion, Abel's case had other complicating features in addition to EPI making diagnosis, treatment, and management difficult. This case shows how GI signs of chronic weight loss and vomiting leads to a long list of differentials. EPI should always be on your differential

list especially with a young dog who fits the clinical signs and typical signalment. A send out GI panel evaluating cTLI is the best and most practical test for definitively diagnosing EPI, and with proper lifelong supplemental therapy, prognosis can be good.

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