Emmie’s Exocrine Error

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Class of 2021

Clinicopathologic Conference

April 16, 2021

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Introduction

Exocrine pancreatic insufficiency (EPI) occurs when the pancreas is unable to adequately produce digestive enzymes due to various causes, and results in the dog being unable to properly absorb nutrients. This leads to typical clinical signs of maldigestion such as polyphagia, weight loss, flatulence, steatorrhea, coprophagia, increased fecal volume, yellowish feces, and poorly digested loose feces.[1,5,11,13,15] There are various pathologic processes that can lead to exocrine pancreatic insufficiency; however, the most common cause is pancreatic acinar atrophy.[1] There are certain breeds predisposed to this disease, and EPI should always be a differential diagnosis when these dogs show clinical signs of maldigestion. Multiple diagnostic tests exist, but canine trypsin-like immunoreactivity test is the most reliable for diagnosing EPI. There are various treatment options, and the best treatment plan varies between dogs. However, all dogs should receive pancreatic enzyme replacements and parenteral cobalamin if they have hypocobalaminemia. Therapy for EPI is lifelong, but the prognosis is good for dogs that respond well to initial therapy.[2,5]

History and Presentation

Emmie, a 4.5-year-old female spayed Labrador Retriever, presented to Mississippi State University College of Veterinary Medicine Community Veterinary Service on September 11, 2019 for a four-week history of diarrhea and intermittent vomiting. Approximately four weeks before presentation, Emmie got into the dog food while her owner was away and ate several cups worth of food. The backyard chicken flock was also dewormed around this time and Emmie is known to eat chicken feces. At this time, her stool was soft, unformed, yellow in color, “bulky,” and contained undigested food particles. She was also coprophagic.

Her owner is a veterinarian and treated her on August 23, 2019 with metronidazole (250 mg) orally for ten days, and Cerenia (60 mg) orally for four days. Her vomiting resolved, but the diarrhea persisted despite treatment. She was then treated on September 3rd with fenbendazole for three days and tylosin for ten days. Once again, her diarrhea persisted despite treatment. Her only other significant health history is a history of urinary incontinence associated with recurrent urinary tract infections.

Upon presentation, Emmie was bright, alert, and responsive. She weighed 29.3 kgs and had an ideal body condition score of 4/9. Her vital parameters were within normal limits with a respiratory rate of 20 breaths per minute, heart rate of 124 beats per minute, and a temperature of 101.1 F. Thoracic auscultation was normal with no crackles, wheezes, murmurs, or arrhythmias noted. Her abdomen was nonpainful on palpation, and all peripheral lymph nodes palpated normally. The remainder of her physical exam was unremarkable.

Pathophysiology

The pancreas is both an endocrine and exocrine gland,[6] however as the name suggests, only the exocrine functions of the pancreas tend to be affected by EPI.[8,14] The exocrine pancreas is responsible for providing enzymes needed for the digestion of carbohydrates, proteins, and triglycerides.[6] These enzymes are produced in the acinar cells of the gland and are secreted into the duodenum where they begin digestion.[6] The exocrine pancreas has a large secretory capacity reserve, so clinical signs of maldigestion do not occur until approximately 90% of exocrine tissue has been lost.[7,11,14,15]

Exocrine pancreatic insufficiency is considered a functional diagnosis based on decreased pancreatic secretion capacity on pancreatic function tests.[14] Many pancreatic diseases such as

pancreatic acinar atrophy (PAA), chronic pancreatitis, pancreatic hypoplasia, and pancreatic neoplasia have been associated with causing EPI.[7,14,15] Of these conditions, pancreatic acinar atrophy is by far the most common cause and pancreatic neoplasia is very rarely the cause of EPI.[14,15] Studies have shown that certain breeds and female dogs are overrepresented when it comes to developing EPI, though it is not well understood why females are more frequently affected.[5,14]

Pancreatic acinar atrophy causes selective destruction of the acinar cells, which leads to inadequate secretion of digestive enzymes and the typical signs of maldigestion associated with EPI.[14,15] PAA is believed to be a progressive degenerative disease based on morphologic findings of the pancreas.[14,15] PAA has been seen in many breeds, however it is most commonly seen in German Shepherds and Rough-Coated Collies.[4,5,8,14,15] In fact, 70% of dogs diagnosed with EPI (which is most frequently due to PAA) are German Shepherds.[15] Genetic susceptibility and histology findings have lead researchers to believe there is an autoimmune component to PAA.[4,8,14,15]

Certain breeds are predisposed to developing exocrine pancreatic insufficiency though the underlying cause differs. As previously discussed, German Shepherd Dogs and Rough-Coated Collies are predisposed to PAA which leads to EPI.[4,5,8,14,15] These dogs usually develop clinical signs of EPI between 1 to 5 years of age; and there are hereditary and autoimmune components associated with their disease.[4,8] Cavalier King Charles Spaniels have also shown an increased risk for EPI with clinical signs usually developing around 7 years of age, suggesting a different pathogenesis for EPI development in this breed.[1,5] In contrast, a retrospective study demonstrated a decreased prevalence of Boxers, Golden Retrievers, Labrador Retrievers, Weimaraners, and Rottweilers with EPI.[1,5]

Diagnostic Approach/ Considerations

EPI is suspected based off of typical clinical signs and histories and is confirmed with pancreatic function tests.[14,15] The most common clinical signs of EPI include yellowish or grey feces, increased fecal volume, increased defecation frequency, weight loss, and flatulence.[15] Other frequent signs include polyphagia, coprophagia, undigested food particles in feces, and loose feces.[14,15] Occasionally, dogs will present with histories of vomiting, intermittent anorexia, and abdominal discomfort.[14] These are all typical signs of malabsorption and not pathognomonic for EPI as they can also be seen in dogs with small intestinal disease.[14]

Routine blood work is usually unremarkable for dogs with EPI. Complete blood counts (CBC) may occasionally reveal a mild lymphopenia and eosinophilia, but they are usually within normal limits.[15] Chemistry panels are usually unremarkable but may reveal mild to moderate serum alanine aminotransferase (ALT) increase, hypolipidemia, and hypocholesterolemia.[15] Surprisingly, dogs with EPI are able to maintain normal serum protein concentrations even when severely malnourished.[15]

Serum canine trypsin-like immunoreactivity (cTLI) test is the gold standard for diagnosing canine EPI as it is species and pancreas specific.[14,15] Healthy dogs have a cTLI greater than 5.7 to 45.2 μg/L; and serum concentrations less than 2.5 μg/L combined with clinical signs of maldigestion are diagnostic for EPI.[14] A benefit of this test is that intestinal disease will not affect TLI because trypsinogen is not absorbed from the intestinal lumen.[15] It is recommended to fast dogs 8-12 hours before sample collection because a slight postprandial increase of serum trypsinogen levels is possible.[15] This is an excellent test for practitioners as only a single sample is usually needed to make a diagnosis of EPI.[15]

There are various tests that examine the fecal proteolytic activity in dogs with EPI. It is common for dogs with EPI to have decreased proteolytic activity; however, normal dogs can also have occasional decreased proteolytic activity.[14,15] These tests need to be repeated as proteolytic activity is variable and the reliability of individual tests varies.[14,15] Because of this, these tests are not used as frequently as TLI tests. The x-ray film digestion test is a simple and inexpensive semiquantitative test to detect protease activity in feces.[3,15] There is a gelatin coating on unexposed x-ray film, and proteases present in normal feces will digest this coating.[3] Failure to digest this coating indicates protease deficiency or exocrine pancreatic insufficiency.[3] False negatives (absence of digestion) and false positives (digestion of gelatin) may be caused by trypsin inhibitors or bacterial proteases respectively.[9] This test cannot give a definitive diagnosis; however, it is a simple and inexpensive screening test that can be performed in general practice for money conscious clients or in shelter situations where money is tight.

Gross and histologic examination of the pancreas is usually unnecessary for patients with EPI; however, if one needs to know the underlying cause of EPI, a histologic examination of the pancreas must be performed.[4,14] In end stage PAA, the pancreas will be thin and transparent on gross examination with minimal normal glandular structure remaining.[14,15] The pancreatic ducts will be clearly visible and fibrosis is usually not present.[14,15] On histologic examination of end stage PAA, normal acinar tissue will not be present, or it will be present only in isolated lobuli.[14,15] Patients with subclinical EPI often have decreased normal pancreatic mass with scattered areas of atrophied tissue on gross examination, and lymphocytic infiltration of the atrophied acinar cells .[14,15] Dogs with chronic pancreatitis will often have a hard, shrunken, and nodular pancreas with adhesions to other abdominal organs.[14]

Exocrine pancreatic insufficiency was our top differential due to Emmie's history, clinical signs, and failure to respond to antibiotic and anthelmintic therapy. However, other causes of maldigestion including small intestinal dysbiosis, infectious enteropathies, and inflammatory enteropathies were given less consideration.

On September 11, 2019, a CBC and a chemistry panel were performed. The CBC was within normal limits. The chemistry panel had a few mild abnormalities including carbon dioxide 18.3 mEq/L (20-28), blood urea nitrogen 5 mg/dl (8-24), osmolality 274 mOsm/kg (280-305), and magnesium 1.5 mg/dl (1.7-2.4), these abnormalities were determined to be insignificant.

A fecal flotation was performed to look for intestinal parasites, and none were found. An x-ray film digestion test was performed on her stool sample and resulted in a failure to digest the gelatin on the film which is indicative of EPI.

Blood was sent to Texas A&M for cobalamin fasting, folate fasting, pancreatic lipase immunoreactivity (PLI) fasting, and TLI fasting tests. The cobalamin test result was <150 ng/L (251-908) which could be caused by various malabsorptive issues including small intestine disease, small intestine dysbiosis, or exocrine pancreatic insufficiency. Her folate results were within normal limits at 12.6 μg/L (7.7-24.4). PLI was within normal limits at 36 μg/L (≤ 200). Her TLI fasting result was 1.3 μg/L (5.7-45.2) which is diagnostic for exocrine pancreatic insufficiency.

On January 27, 2020 Emmie presented to Mississippi State University College of Veterinary Medicine Community Veterinary Service for incision dehiscence and infection from a gastropexy that she underwent on January 23, 2020 at a different clinic. Emmie was transferred to the surgery service and underwent surgery on January 27, 2020 where a gastrotomy was

performed to remove an incidental foreign body from her stomach, her gastropexy was revised, her incision was debrided, and an abdominal exploratory was performed. During this surgery, it was noted that there was no identifiable pancreatic tissue in the location of the right limb of the pancreas, and there was markedly hypotrophic or atrophied pancreatic lobules in the left limb of the pancreas along the stomach. No samples were taken for histology, but the gross findings were consistent with PAA.

Treatment and Management Options

There is no cure for canine exocrine pancreatic insufficiency and therapy requires lifelong management. There are various therapy options for EPI including pancreatic enzyme replacement, dietary modification, cobalamin supplementation, and occasionally adjunctive therapies.[5] The ideal therapy varies among dogs, but most will require a combination of therapies.

Pancreatic enzyme replacement is the cornerstone of treatment for EPI. This supplement can be given in many forms including raw pancreas, enteric-coated tablets, capsules, granules, or uncoated powder.[2] Multiple studies have been performed to determine the best pancreatic enzyme supplement and have had conflicting conclusions. One study showed that raw pig pancreas and powdered enzyme supplements were the most effective.[14] Whereas a different study found no difference in clinical response between dogs given uncoated supplements vs enteric-coated supplements.[2] Another study found that both enteric-coated and uncoated enzyme supplementation improved clinical signs; but dogs receiving an enteric-coated product responded better to treatment than dogs receiving an uncoated product.[7] Although pancreatic enzyme supplementation is generally well tolerated and improves clinical signs in most dogs, one study

did find that a few dogs developed dose dependent oral bleeding when being fed a powdered pancreatic supplement.[10]

Dogs with EPI are at a high risk for hypocobalaminemia due to decreased intrinsic factor production which is necessary for cobalamin absorption in the ileum.[2,12] A study was performed looking at prognostic indicators for EPI in dogs and found that hypocobalaminemia is a strong poor prognostic factor.[12] Dogs with a serum cobalamin level <100 ng/L did not have a worse response to initial therapy than other dogs, but they did not survive as long as dogs with a cobalamin level ≥ 100 ng/L.[2] Because of this, it is important that cobalamin levels be confirmed at diagnosis of EPI and any patient with hypocobalaminemia be started on parenteral cobalamin supplementation.[2,12] The currently recommended dose of cobalamin is 250-1000 μg, depending on the size of the dog, administered subcutaneously weekly initially and then monthly.[14] It is recommended to monitor cobalamin levels in dogs with EPI that do not initially present with hypocobalaminemia as they may develop it in the future.[5]

Various studies examining the effect of diet on clinical signs have been performed on dogs with exocrine pancreatic insufficiency, and no single diet modification has been determined to be the best for all patients. Historically, low fat diets have been recommended for dogs with EPI due to pancreatic lipase being needed for fat digestion.[5] However, these are low calorie diets and make it difficult for patients to gain and maintain weight.[5] One study showed that feeding a fat supplemented diet in combination with appropriate enzyme replacement therapy improved fat absorption and weight gain in dogs with EPI; which is similar to recommendations for humans with EPI.[5] A study was performed comparing the effect of dogs' normal diet, a high fat diet, a high fiber diet, and a highly digestible low-residue diet on their clinical signs.[13] This study showed no significant improvement or worsening of overall clinical signs for any single diet;

however, individual dogs had significant variability of clinical signs to the different diets.[13] Overall, dogs seemed to perform the best on their initial diet (which varied between dogs), had worse steatorrhea on the high fat diet, and had increased fecal volume and firmer feces on the high fiber diet.[13]

Once diagnosed with EPI, Emmie was started on 1/8th teaspoon of PancreVed powder, which is an enzyme supplement, twice daily. She also started receiving cobalamin injections at a dose of 25 μg/kg administered subcutaneously once weekly. She continued receiving her normal diet of mixed Hill's j/d and i/d. She did well on this treatment regimen and once her diarrhea resolved, her cobalamin injections were decreased to 25 μg/kg once monthly.

Case Outcome/Prognosis

Emmie continued to do well on her treatment plan until December 2020. At this time, Emmie started to relapse. Her diarrhea returned and she was losing weight. Increasing her dose of PancreVed powder did not improve her clinical signs. In January 2021, she was swapped to PancreVed chewable tablets. Emmie's clinical signs worsened significantly while on the PancreVed tablets and she lost 9 lbs between December 2020 and March 2021. Her cobalamin injections were also increased to once weekly during this time. At the beginning of March 2021, her enzyme supplement was swapped to Viokase-V powder. She currently receives 1/8th teaspoon of this supplement twice daily with her meals. She receives 25 μg/kg of cobalamin subcutaneously once weekly and will remain on this dose until her clinical signs improve.

Emmie's owner reports that she has been slowly improving since swapping to the Viokase-V enzyme powder at the beginning of March. Since swapping products, Emmie has gained 2 lbs and her stool is slowly improving.

It is not uncommon for some dogs to remain underweight or continue having diarrhea despite treatment.[5] Therefore, it is important to educate owners that this is a lifelong disease and that their pet may continue having some clinical signs despite treatment. Studies have shown that dogs that have a good response to initial therapy have a good prognosis for long term survival with a median survival time of greater than 5 years.[2,5]

Conclusion

Exocrine pancreatic insufficiency should be considered as a differential diagnosis in dogs displaying clinical signs of maldigestion, especially in breeds predisposed to EPI. EPI can be caused by a variety of diseases that affect the exocrine pancreas, but pancreatic acinar atrophy is by far the most common cause, particularly in German Shepherds.[1,4,14,15] To confirm a diagnosis of EPI, a canine TLI test should be performed. The ideal treatment protocol varies among individual dogs, but it should always involve pancreatic enzyme supplementation along with parenteral cobalamin if hypocobalaminemia is detected. Therapy is lifelong and may have to be adjusted from time to time. Dogs with hypocobalaminemia have a poorer prognosis, but dogs that survive the initial therapy period have a good long term progniosis.[2,5]

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