Care of dogs with protein-losing enteropathy (Proceedings)

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Protein-losing enteropathy (PLE) is defined as the loss of protein from the intestines due to intestinal disease. Often, this results in a decreased serum albumin concentration (hypoalbuminemia), sometimes this is accompanied by a decreased serum globulin concentration (hypoglobulinemia). Strictly, any condition leading to abnormal protein loss from the intestines is a PLE. However, if the patient's serum albumin is not decreased, this protein loss often goes un-noticed. Any intestinal disease, if severe enough, can result in PLE. The underlying mechanism for this is disruption of the intestinal lining (the mucosal barrier). Because a number of diseases can lead to this disruption, PLE is classified as being a syndrome rather than a disease. PLE is much more commonly diagnosed in dogs than cats. Diseases that have been found to cause PLE in dogs include: intestinal lymphangiectasia (IL), inflammatory bowel disease (IBD), intestinal cancer (neoplasia), gastrointestinal ulceration, fungal infections, intussusception, and gastrointestinal parasites. Protein losing enteropathy can lead to some important consequences in our patients, which can even be life threatening.

Clinical presentation

Due to the diverse range of underlying conditions that cause PLE, any age, breed, or sex of dog may develop PLE. However, some breeds have been demonstrated to be particularly at risk. These include Yorkshire Terriers, Soft Coated Wheaten Terriers, Norwegian Lundehunds, and Basenjis.

The most common clinical signs of PLE in dogs are diarrhea, vomiting, and weight loss. It is important to remember that some dogs with PLE may not vomit or have diarrhea, these dogs usually but not always present with weight loss. Other clinical signs may be due to the loss of serum proteins, especially albumin. They include ascites, edema and pleural effusion. This is because albumin is largely responsible for holding fluid within the blood vessels, by contributing to the intravascuclar oncotic pressure. Low blood oncotic pressure can lead to accumulation of fluid outside of the blood vessels. Occasionally, dogs suffering from PLE develop respiratory

distress due to a blood clot moving to their lungs (pulmonary thromboembolism). During PLE, blood proteins including the proteins that stop the blood from spontaneously clotting are lost into the intestines. The most important of these is called antithrombin. When the antithrombin level drops significantly below normal, dogs are at risk of developing spontaneous blood clots called thrombi.

Physical examination may reveal weight loss and poor body condition due to malnutrition. Thoracic auscultation may reveal decreased lung sounds due to pleural fluid. Swelling of the legs and/or ventral parts of the body due to edema may be present. Abdominal palpation may reveal a fluid wave, abdominal masses, enlarged organs, enlarged lymph nodes, or thickened bowel loops.

Diagnostic approach

As discussed before, many animals with PLE have non-specific signs of gastrointestinal disease. However, some dogs will present with weight loss alone or decreased serum albumin may even be noticed as an incidental finding. Signs of decreased albumin, such as edema and ascites can also be present. A serum biochemistry panel will confirm hypoalbuminemia. Many references state that both albumin and globulin are consistently decreased in dogs with PLE. In reality, the globulin concentration can be decreased, normal, or increased, so it is the albumin concentration that is more important to consider.

Once hypoalbuminemia has been documented it is tempting to diagnose PLE in any dog with gastrointestinal signs. However, there are other possible causes of hypoalbuminemia and these can be associated with clinical signs of diarrhea, vomiting, and weight loss. The possible causes of a serum albumin concentration below 2.0 g/dL are failure of the liver to produce albumin (hepatic insufficiency), loss due to severe dermatological disease, loss from the kidneys (protein losing nephropathy), or loss from the intestines (protein losing enteropathy). To diagnose PLE, the three other possible causes should be ruled out or increased fecal protein loss should be demonstrated. The possibility of liver disease is investigated by interpretation of a serum chemistry panel and possibly performing a bile acid stimulation test. The presence of severe dermatological disease is easily determined during physical examination. Protein losing nephropathy is investigated by measuring the amount of protein in the urine. This can initially be done by urinalysis. If urinary protein loss cannot be ruled out this way, a urine protein to creatinine ratio should be performed.

Once PLE has been confirmed, it is important to realize that this is a syndrome and not a diagnosis. Efforts should be made to find the underlying cause. Abdominal ultrasound is frequently the most useful imaging modality for assessing the gastrointestinal system of small

animals. Changes on abdominal ultrasound can often be observed with PLE patients, but these seldom give us a definitive diagnosis. Microscopic evaluation of intestinal biopsy specimens is often the most informative test. Intestinal biopsies can be collected via endoscopy, via an open abdominal surgery, or via “keyhole” surgery of the abdomen (laparoscopy). Each technique has its advantages and disadvantages. At Texas A&M, endoscopy is often performed initially. It is very important to perform an upper and lower gastrointestinal tract endoscopy so that the stomach, duodenum, ileum, and colon can all be biopsied. In most cases when combined with the clinical presentation, laboratory tests and imaging findings, histopathologic analysis of endoscopic intestinal biopsies can lead to at least a provisional diagnosis, and guide initial treatment. However, sometimes a final diagnosis is only made after assessing the patient's response to treatment.

Generally 8–12 specimens are collected from each region of the gastrointestinal tract. Meticulous handling of endoscopic biopsy specimens is essential to optimize the diagnostic value of this procedure. Once collected fine gauge needles should be used to transfer the biopsy specimens to a histopathology sponge that has been pre-dampened with saline. The needles should be used to gently unfold the specimen with the luminal side facing upwards. It is also beneficial for the person handling the specimens to give the endoscopist feedback with regards to the adequacy of the specimens. The specimens from each anatomical section of the GI tract are then placed in separate containers containing an adequate volume of neutral buffered formalin and sent for processing and analysis.

Common causes

Although any intestinal disease that is severe enough to cause loss of the mucosal barrier function can result in PLE, some diseases are commonly recognized to cause PLE.

Intestinal lymphangiectasia is characterized by dilation of the lymph vessels of the intestines. It is believed to be the most common cause of PLE in dogs. IL occurs in both a congenital form (primary IL) and an acquired form (secondary IL). Primary IL is a developmental abnormality that leads to an insufficiency or malformation of the lymphatics. This condition may affect other parts of the body as well as the intestines. Secondary IL is due to obstruction of lymph flow. This develops either due to physical blockage of the lymphatics, or high venous pressure. The lacteals may be physically blocked by inflammation or cancer of the intestines. When the lymph flow is obstructed, high protein lymph leaks out into the intestinal wall. This leakage of protein contributes to the intestinal disease. Yorkshire Terriers, Maltese Terriers, Rottweilers, and Norwegian Lundehunds are predisposed to primary IL. The diagnosis of IL is based on documenting a PLE, finding lesions consistent with IL on histopathologic evaluation of

intestinal biopsies and ruling out other underlying causes, such as heart failure. During endoscopy, distended lacteals may be visible as multiple white spots on the intestinal mucosa.

Inflammatory bowel disease (IBD) is defined as chronic inflammation of the bowel wall. Idiopathic IBD is diagnosed on the basis of observing inflammatory cell infiltrates in the bowel wall on intestinal biopsies and ruling out other causes for the inflammation. These other causes include dietary intolerance or allergy, antibiotic responsive enteropathy (intestinal disease), and parasites. In idiopathic IBD, inflammatory cells accumulate in the bowel wall for an unknown reason. The inflammation is often classified according to which cell types are most abundant. Lymphoplasmacytic inflammation is the most commonly identified variety of IBD in dogs and cats. IBD must be severe in order to result in intestinal protein loss.

Certain breeds of dog are predisposed to getting distinct forms of PLE. Soft Coated Wheaten Terriers often develop a hereditary PLE characterized by IL and inflammation of the intestinal wall with a concurrent protein losing nephropathy. Basenji's can develop what is described as an immunoproliferative enteropathy. Lundehund syndrome is characterized by gastritis, IL, and IBD.

Lymphoma is a common cancer arising from a type of white blood cells called lymphocytes. Lymphoma can affect many parts of the body, including the intestines. Roughly 75% of dogs with intestinal lymphoma will have hypoalbuminemia. Lymphoma can be diagnosed based on intestinal biopsies, although endoscopic biopsies may not be deep enough to distinguish this cancer from intestinal inflammation. Laboratory tests such as immunophenotyping and PCR for antigen receptor rearrangements can help differentiate lymphoma from IBD. Adenocarcinoma and other tumors may also cause PLE due to blood loss and mucosal ulceration. These tumors may be confined to one section of the intestine. Because of this it may not be possible to reach them with an endoscope. Consequently, surgical biopsy or fine needle aspiration of any mass that is present may be required. Abdominal ultrasound can help in selecting which sampling technique is best to use.

Histoplasma capsulatum is a fungal organism that can cause gastrointestinal disease in dogs and cats. It is unusual for Histoplasma to affect the gastrointestinal tract of cats, but it is reasonably common in dogs. Diagnosis can often be made on cytological evaluation of rectal scrapings, lymph node aspirates, hepatic aspirates, or splenic aspirates, depending upon which organs are affected. Occasionally the diagnosis is made on intestinal biopsy, but this is not usually necessary. A urine/serum antigen test (Histoplasma EIA, Mira Vista Laboratories) is also available.

Treatment

As there are many underlying causes of PLE in our patients there is no single treatment protocol for this syndrome, every patient has different needs. The aims of therapy are to treat the underlying cause and to support the patient. Treatments of IL and IBD as well as supportive care are discussed below.

The mainstay of treatment for IL is feeding an ultra low fat, highly digestible diet. Reducing the dietary fat content decreases the amount of fat that needs to be transported in the intestinal lacteals, thereby to some extent reducing the problem of the lacteal obstruction. The commercial diets with the lowest fat contents are Royal Canin Digestive Low-Fat and Hill I/D Low-Fat. An alternative is to use a diet of boiled fat free turkey and rice. This home cooked diet is very low in fat and it may also be beneficial for dogs with dietary intolerance or allergies. This diet can be used initially and if the patient responds after 2–3 weeks, it must be supplemented in order to make it nutritionally balanced. Commercial weight-loss diets are not suitable for dogs with PLE because although they have a fairly low fat content they are calorie restricted and usually these dogs are already severely malnourished. Some very sick PLE patients may benefit from being fed an elemental diet such as Vivonex T.E.N. Elemental diets are very low in fat and very easy to digest, as they contain amino acids rather than proteins. They are expensive and so are typically used to provide short-term nutrition. In some cases of IL there is a component of inflammation, which can be the primary problem or can occur secondary to leakage of protein rich fluid. The presence of inflammation is determined by evaluation of intestinal biopsy specimens. If this is the case, the patient may benefit from anti-inflammatory medications. Common choices are prednisone, azathioprine, and cyclosporine.

As previously discussed, IBD must be severe in order to cause PLE. Consequently, aggressive treatment is needed. Anti-inflammatory drugs are the main treatment for IBD. Common choices are prednisone, azathioprine, and cyclosporine. Prednisone and prednisolone are the most commonly used anti-inflammatory drugs for treating IBD, and are cheap and frequently effective. However, these drugs often have unwanted side effects when used at higher doses. Azathioprine is often used in conjunction with prednisone to provide additional immunosuppression, or so that a lower dose of prednisone can be used. This drug can have serious side effects (it can affect the liver and the bone marrow) and should NOT be used in cats. Furthermore, it takes up to 2 weeks of treatment before it is fully effective. This is an important consideration for a sick patient. Cyclosporine is a newer immunosuppressive agent that is generally well tolerated and acts quickly. It is expensive, especially for larger dogs, and there is currently much data to support its use in IBD, although the preliminary data is encouraging. Dietary management is also important in dogs with IBD. Often dogs with IBD and PLE have not undergone a diet trial prior to biopsy, so a diet trial with a novel antigen or hydrolyzed antigen

diet is frequently worthwhile. However, if microscopic evaluation of the intestinal biopsies suggests or confirms a diagnosis of IL, I advise feeding an ultra low fat diet.

Supportive care

Because of their hypoalbuminemia, gastrointestinal disease, and their potential to develop spontaneous blood clots PLE patients are fragile. Supportive care is therefore extremely important.

Providing adequate nutrition is vital. Patients, who are vomiting or have severe gastrointestinal disease, may not willingly eat. Often, treatment of nausea with anti-emetics such as maropitant (Cerenia) is the first step to take. If this is not effective, tube feeding may be needed. In small to medium sized dogs an esophageal feeding tube is my preference, whereas I typically place gastrostomy tubes endoscopically in larger dogs, and in giant breeds or deep chested breeds surgical placement of a gastrostomy tube may be needed. Forced syringe feeding is not a practical longer-term solution. The dog's resting energy requirement (RER) should be estimated using the following formula: RER (kilacalories) = bodyweight (kg) 0.75. For patients that have been anorexic for more than two days it is advisable to feed ½ the estimated RER during the first 24 hours before increasing to the full amount the next day if feedings are well tolerated. With emaciated dogs eventually it is important to feed more calories than the estimated RER so that they gain weight. One method is to estimate a target weight for the dog and feed the RER calculated based on this. The total amount of food for that day should be divided into 4–6 meals. Although it is time consuming these meals should be fed slowly over 10–20 minutes. If the patient vomits or appears nauseous it can be helpful to warm the food to approximately body temperature or feed it as a continuous rate infusion using a syringe pump.

When necessary administration of intravenous fluids that provide oncotic support can help reduce fluid accumulation and therefore stabilize the dog's circulation. This can be especially important prior to or during anesthesia. However, often these dogs have had chronic hypoalbuminemia and so they have compensated for their low blood oncotic pressure and do not require colloidal support. Synthetic colloids (such as Hetastarch) are currently my preference for providing colloidal support to dogs with PLE. Human albumin solutions are available and are sometimes used in severely hypoalbuminemic dogs but can be associated with severe side effects due to immune reactions. Plasma transfusion is not a practical way to provide increase a dog's serum albumin in most cases as relatively large amounts need to be given, which for all but very small dogs is cost prohibitive.

Measures to reduce the risk of thrombosis include giving ultra-low dose aspirin (0.5 mg/kg PO q24 hrs) or clopidogrel (Plavix; 1–3 mg/kg PO q24 hours), meticulous care of IV catheters, not

placing unnecessary IV catheters, and frequently encouraging the patients to move.

Dogs with PLE often have low serum vitamin B12 (cobalamin) concentrations as they cannot absorb this vitamin from their small intestine. Supplementing cobalamin by subcutaneous injection can correct this, and may improve the patient's gastrointestinal signs, as well as their appetite. It is important to use injectable cyanocobalamin and not injectable vitamin B mixtures, as these do not contain sufficient cobalamin.