Protein-Losing Enteropathy: The Beginning of the End?

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Intestinal protein loss is a sign of failure of digestive function that may result from severe acute or chronic inflammatory lesions or from a disruption of chyle absorption and intestinal lymph flow. While the exact mechanisms leading to intestinal protein loss have not been elucidated in the dog, the three basic mechanisms defined for humans with protein-losing enteropathy (PLE) likely also apply to canine PLE. Protein loss may result from 1) erosive or ulcerative mucosal lesions causing secondary exudation of proteins; 2) lymphatic dysfunction causing leakage of protein rich lymph into the intestinal lumen; and/or 3) mucosal changes disturbing the "mucosal barrier", causing abnormal permeability and protein leakage into the lumen.[1]

This presentation will focus on chronic intestinal disorders associated with intestinal protein loss in dogs. PLE is much less prevalent in cats. In dogs, it is frequently associated with severe chronic idiopathic inflammatory enteropathies such as inflammatory bowel disease (IBD) or with idiopathic intestinal lymphangiectasia in specific breeds.

Objectives

- To describe a systematic diagnostic approach to confirm the intestinal protein loss and identify the cause of the problem
- To review the main causes of protein-losing enteropathy (PLE) in dogs
- To provide updated therapeutic options and discuss the prognosis of various forms of PLE

Diagnostic approach

Dogs with PLE often present with typical clinical signs of chronic intermittent small intestinal diarrhea with possible vomiting. In severe cases, dysorexia/anorexia and malnutrition with evidence of malabsorption and weight loss may be observed. However, significant intestinal protein loss and hypoalbuminemia may also occur without obvious diarrheic episodes. In some dogs, hypoalbuminemia may even be detected incidentally during regular heath screens. In the presence of severe hypoalbuminemia (serum albumin < 20 g/l, often ≤ 15 g/l) the main complaint may relate to signs suggestive of significantly decreased oncotic pressure (cavitary effusion, subcutaneous edema).

The first diagnostic challenge consists in establishing the origin of the protein loss. To this effect, a minimal diagnostic database should be collected (CBC, chemistry panel, urinalysis). Renal protein loss must be ruled out (urinalysis, urine protein-creatinine ratio), as well as liver dysfunction (postprandial serum bile acids). Additionally, third spacing of serum proteins should be considered (e.g. vasculitis). Generally, PLE is associated with panhypoproteinemia due to non-selective protein loss. Hypoalbuminemia with normal or increased globulin concentration is suggestive of protein-losing nephropathy or possibly liver dysfunction. While these rules of thumb are useful in practice, they should not be blindly relied upon since many exceptions occur. For instance, a dog with significant systemic inflammation may present with hypoalbuminemia and hyperglobulinemia. Other common abnormalities of dogs with PLE include hypocholesterolemia, hypocalcemia (total and ionized), hypomagnesemia, and lymphopenia.

Once the GI tract has been confirmed as the site of protein loss, further work-up should include abdominal ultrasound with a particular focus on the intestinal wall, in particular wall thickness and wall layering. The ultrasonographic appearance of the intestinal wall consists of 5 distinct layers. Hyperechogenic mucosal striations are frequently observed in dogs with PLE, and appear to be quite specific. It has been postulated that they may represent dilated lacteals although they may also be due to dilated crypts often seen in PLE or to other mechanisms. Striations should not be confused with hyperechogenic mucosal speckles that are only a non-specific indicator of inflammation.

However, the final diagnosis relies solely on histopathologic analysis of intestinal biopsies collected during endoscopy or exploratory laparotomy. Dogs with severe hypoalbuminemia are poor anesthetic candidates, and it is sometimes preferable to avoid taking excessive risks and postpone endoscopy or surgery. Additionally, many dogs with PLE have bicavitary effusion, and thoracic radiographs are recommended as a screening tool for the presence of thoracic effusion, which may represent an additional anesthetic risk. Synthetic (hydroxyethylated starches) and natural colloids (plasma, human or canine albumin concentrates) are very useful in order to acutely increase oncotic pressure in critical cases. In spite of the risk of anaphylactic reaction or other complications, slow transfusion of 5% human albumin at 2 ml/kg/h during 10 h/day (total daily volume of 20 ml/kg/day) has been successful for partial restoration of serum albumin concentration in order to minimize the risks of general anesthesia.

The decision regarding the preferred biopsy collection technique depends on a variety of factors such as availability of the equipment and surgical or endoscopic skills of the veterinarian. Advantages of a surgical exploration include the possibility of sampling several sites along the small intestine and obtaining full thickness specimen. Surgical collection of intestinal biopsies was not shown to be more risky in hypoalbuminemic patients, although a cautious approach is recommended (consider serosal patching). Endoscopy allows relatively non-invasive collection of biopsies limited to the mucosa, and good endoscopic skills are required to obtain quality specimen. However, visualization of the mucosa is an advantage, and allows targeted sampling of mucosal lesions.

Traditionally, only the duodenum was examined. Recent studies convincingly demonstrated that collecting both duodenal and ileal biopsies is essential, as lesion distribution may be irregular and severe ileal lesions may occur in a dog with only mild (or absent) duodenal lesions. This added procedure may prolong anesthesia time since a colonoscopy is required to intubate the ileum or at least collect ileal mucosal biopsies by blindly passing a forceps through the ileo-colic junction. However, the improved diagnostic yield often outweighs the inconvenience of a prolonged procedure.

Differential diagnosis

Diseases frequently associated with PLE include intestinal lymphangiectasia, _ENREF_2_ENREF_2IBD, and chronic enteropathies characterized by significant mucosal architectural changes such as dilation of small intestinal crypts. Moreover, alimentary lymphoma and fungal infections (histoplasmosis) may also cause PLE._ENREF_1

Intestinal lymphangiectasia (IL): The following breeds have been shown to be prone to primary IL: Yorkshire terriers, Chinese shar-peis, Maltese terriers, Norwegian lundehunds, and Rottweilers (in Europe). The pathogenesis of primary IL is still poorly understood. It results from obstruction to the flow of lymph in the intestinal wall, which could conceivably be due to abnormal intestinal lymphangiogenesis. However, acquired obstruction to normal lymph flow appears to be a more common occurrence, in the form of granulomas associated with lymph leakage impinging on intestinal lymphatics, and/or intestinal lymphangitis. Secondary IL is commonly associated with significant intestinal mucosal inflammation (e.g. IBD) and neoplasia (alimentary lymphoma). Histopathologic mucosal changes include dilated lacteals in the mucosa, and deep-seated perilymphatic granulomas that can be seen in full thickness biopsies. Lacteals are essential for fat absorption and their obstruction leads to severe dilation and tear. Damaged lacteals empty their lipid- and protein-rich content into the intestinal lumen.

Inflammatory Bowel Disease (IBD): The term IBD describes “a group of chronic enteropathies characterized by persistent or recurrent gastrointestinal (GI) signs and inflammation of the GI tract” (from ref. 12). The inflammatory process located in the GI mucosa may lead to protein loss both by preventing the absorption of nutrients and by compromising the integrity of the intestinal mucosal barrier leading to exudation of proteins into the intestinal lumen.

PLE of soft-coated wheaten terriers is a specific form of IBD affecting this breed worldwide. In approximately 50% of these dogs, PLE and protein-losing nephropathy (PLN) occur concurrently. Mucosal lesions can be severe and include inflammatory infiltration, dilated lacteals, and deep-seated intestinal lymphangitis. While the pathogenesis is still poorly understood, a hypersensitivity component has been documented as specific proteins can trigger clinical episodes.

Crypt disease: Crypt dilation and necrosis have been frequently associated with PLE. Crypt dilation is a mucosal architectural change that is relatively frequently observed in dogs with IBD and IL. However, in some cases, crypt dilation and abscesses may be the only detectable mucosal lesions in dogs with PLE. In a recent study of 58 dogs with chronic enteropathies, the author’s group showed that dogs with histologically documented small intestinal crypt abscesses are more likely than dogs with no such lesions to experience significant hypoalbuminemia due to PLE, to show ultrasound changes of their intestinal mucosa, and to experience more severe clinical signs.

Therapy

The two main components of treatment in dogs with PLE are dietary modification and management of the inflammatory process.

Diet : Dogs with PLE are in a catabolic state, and adequate nutrition is essential. There are currently no published studies critically evaluating nutritional aspects of canine PLE. However, a large body of clinical experience is available. In dogs with *primary idiopathic IL*, dietary modification centers on feeding a highly digestible diet with low to very low fat content (10-15% on a dry matter basis) to prevent further dilation and rupture of lacteals. Additionally, the diet should contain highly bioavailable dietary proteins and be low in crude fiber. While drug therapy may be administered for a few months (see below) and then discontinued in some cases, dietary therapy should probably be maintained for the length of the dog’s life. In dogs with *PLE associated to underlying IBD*, many veterinary gastroenterologists report good success with exclusive feeding of a diet consisting of hydrolyzed proteins. Novel protein diets are an alternative approach.

Acceptance of the diet is a critical issue in PLE dogs, particularly in the most severely affected animals, which may be anorexic. For each patient, the veterinary care team needs to identify the most palatable diet. Initially, it might be more important to feed a less optimal diet that the dog will be interested in eating, and progressively transition to a more desirable diet.

Management of inflammation: In dogs with primary IL, anti-inflammatory glucocorticoid therapy (e.g. prednisone at 1 mg/kg/day) is useful and often required for proper management of the disease. Its main desired effect is to decrease inflammation associated with lipogranulomas secondary to chyle leakage and therefore help restoring an adequate flow in intestinal lymphatics. In some dogs, anti-inflammatory treatment can be slowly weaned of over 2-3 months or longer.

Immunosuppressive therapy: Immunosuppression is the basis for treatment of severe IBD with PLE. As a side note, it is important to remember that chronic immunosuppression may make animals more susceptible to developing severe infections after contact with pathogens or opportunistic microorganisms.

The first approach consists of administering *prednisone* or *prednisolone* using the following protocol: start with 2 mg/kg q12 h during 3-5 days, then switch to 2 mg/kg once daily until the dog's condition has significantly improved and appears stable. Subsequently the dose can be decreased in 2-week steps with 1 mg/kg/day, then 1 mg/kg every other day and so on. However, side effects of steroid therapy may compromise owner's compliance.

Other corticosteroids: *budesonide* has gained in popularity in the treatment of canine IBD. In humans, the drug is known to be locally efficient and undergo high first pass hepatic metabolism. Therefore, systemic complications of steroid treatment are less likely. In dogs, the drug significantly influences the pituitary-adrenal axis. To date, budesonide use in dogs or in cats with IBD has not been evaluated critically and only anecdotal reports are available. Furthermore, there is no data on the pharmacokinetics of the orally administered drug in pets. The recommended doses are 0.5-3 mg/dog daily (depending on the dog's size). The drug needs to be reformulated by a compounding pharmacist for use in small dogs. Concurrent use with other glucocorticoids is not recommended.

Azathioprine is a thiopurine drug that may be used in dogs with steroid-refractory IBD, and in those that relapse when prednisone treatment is weaned off. It may also be combined with prednisone in the initial treatment of severe cases of IBD. Azathioprine is generally well tolerated, but side effects include bone marrow suppression, hepatotoxicity and pancreatitis. Regular monitoring of CBC and biochemistry profile is advisable during the first weeks to months of treatment. The initial dose is 2 mg/kg daily for 3 weeks, then 1-2 mg/kg every 48 h. Up to 3 weeks of treatment may be necessary for the drug to reach maximal effect.

Chlorambucil is an alkylating agent. It is mostly used in conjunction with prednisolone in cats with low-grade alimentary lymphoma or refractory IBD. A recent study from the UK compared the survival of 27 dogs with chronic enteropathies and PLE with serum albumin concentration < 18 g/l receiving a prednisolone and chlorambucil combination (n=14) versus that of dogs treated with prednisolone and azathioprine (n=13). At recheck, dogs receiving chlorambucil and prednisolone had gained more weight and their serum albumin concentration was significantly higher than in the other group. Also, the survival was greatly improved using the chlorambucil combination. The recommended initial canine dose of chlorambucil is approximately 4 mg/m^2 q24-48h, and it comes in 2 mg tablets (the drug will need to be appropriately reformulated or compounded for small dogs). Side effects of chlorambucil are rare and include bone marrow suppression. A CBC should be performed after 1 and 3 weeks of treatment and repeated every 2-3 months or if the dog's condition deteriorates to look for neutropenia.

Cyclosporine is an inhibitor of T-cell function. Pharmacokinetics of cyclosporine in dogs with IBD do not appear to be significantly different from those of normal dogs. In a clinical study more than half of dogs with steroid-refractory IBD went into complete remission within 4 weeks of cyclosporine treatment (5 mg/kg PO once daily). Additionally, several dogs experienced partial remission. Transient adverse effects were seen during the first 2 weeks of treatment in approx. ¼ of the dogs and included vomiting and loss of appetite, hair coat changes, and gingival hyperplasia. Most side effects responded to temporary discontinuation followed by dose-reduction. Most responders remained free of clinical signs after discontinuation of cyclosporine treatment. Monitoring of whole blood or plasma concentration of cyclosporine is controversial and rarely performed. In dogs that regularly vomit 1 to 2 h. after oral administration, it is possible that serum cyclosporine concentration peak reaches toxic levels, and splitting of the daily dose may be beneficial.

Other immunosuppressive drugs such as mycophenylate mofetil, methotrexate and leflunomide have been used to treat immune-mediated or autoimmune diseases in dogs. Due to lack of data and possible side effects on the intestinal mucosa, their use for treatment of IBD in dogs cannot be recommended at this time.

Complications

Hypocobalaminemia: Low serum cobalamin (Vitamin B12) concentrations are commonly found in dogs with PLE, especially in the presence of underlying IBD. Deficiency in vitamin B12 has negative effects on the intermediary metabolism and may delay proper healing of intestinal inflammation. Hypocobalaminemic dogs are initially treated with weekly SC injections of vitamin B12 (from 250 to 1500 µg/dog based on body weight) for 6 weeks. If the treatment is successful, the interval between injections may be increased to 2 weeks for another 6 weeks.

Hypercoagulability: Recent studies using thromboelastography have revealed the high prevalence of hypercoagulability in dogs with PLE, which significantly increases the risk of potentially fatal thromboembolic events. The problem may be compounded by the pro-thrombotic effects of glucocorticoids which are often used for treatment. Interestingly, hypercoagulability does not appear to resolve after successful treatment of PLE, and this raises questions as to the pathogenesis of this complication. In dogs with documented hypercoagulability, administration of low doses of aspirin (0.5-1 mg/kg/day) and/or clopidogrel (1-5 mg/kg/day) should be considered in order to prevent thrombosis. However, there is currently no study confirming the beneficial effect of such a therapeutic regimen.

Hypocalcemia: A significant decrease of total calcium is expected in dogs with moderate to severe hypoalbuminemia since 50% of total calcium is bound to albumin. However, ionized calcium may also be abnormally low in dogs with PLE. Low serum ionized calcium concentration occurred in association with low 25-hydroxyvitamin D and increased levels of parathyroid hormone in a recent series of dogs with PLE. The authors of the study postulated that hypovitaminosis D was due to intestinal loss rather than to malabsorption since a control group of dogs with IBD without PLE had normal 25-hydroxyvitamin D levels, and serum 25-

hydroxyvitamin D concentration correlated with serum albumin concentrations. Correction of moderate to severe hypocalcemia with parenteral administration of 10% calcium gluconate (e.g. 1 ml/kg slowly IV over at least 15 to 30 min ; may also be administered SC after 1:1 dilution with saline to a maximum daily amount of 9 ml/kg given in 3 to 4 doses) and vitamin D is advisable in order to prevent the onset of clinical signs. Concurrent hypomagnesemia may compromise the success of treatment and should be corrected.

Prognosis

In two European studies encompassing a total of 150 dogs with chronic enteropathies, hypoalbuminemia (serum albumin < 20 g/l) was associated with a less favorable outcome. This was confirmed in a preliminary report from a recent North American study, although outcome did not appear to be correlated to severity of hypoalbuminemia.

Idiopathic intestinal lymphangiectasia: Preliminary reports from a few studies show a high mortality among Yorkshire terriers with IL (50-60%). However, results from the UK revealed that the presence of dilated lacteals was associated with a better outcome in a group of 27 dogs with PLE. In the author's practice, a significant proportion of Yorkshire terriers with IL respond well to a strict diet alone or with anti-inflammatory doses of glucocorticoids. The proportion of refractory cases seems to vary according to geographical location. Unfortunately, to this day, there are no known parameters that allow early segregation of dogs likely to be refractory to dietary and steroid treatment. This would be useful to initiate early aggressive treatment in difficult cases.

Crypt disease: In a series of 58 dogs with chronic enteropathies, the author's group found that the presence of crypt abscesses in the small intestine was associated with significantly shorter survival.

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