Canine Protein Losing Enteropathies

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ABSTRACT

Protein-losing enteropathies are traditionally thought of as being diseases with a very poor prognosis. While this is often true, there are subsets of these patients which, if diagnosed in a timely fashion, may often have a relatively good prognosis. Lymphangiectasia in particular is a disease that is often misdiagnosed or diagnosed so late that it is no longer treatable. Clinicians should actively seek for evidence of lymphangiectasia in dogs with protein-losing enteropathies as this can be a disease that they may be able to control for years, at least in some cases.

Keywords: Canine; Lymphangiectasia; Hypoalbuminemia; Diagnosis

REVIEW

While relatively uncommon in human medicine, protein-losing enteropathies (PLE) are actually relatively common in dogs (1). Historically, they have tended to be associated with severe diseases, and were considered to have a poor prognosis. (2) However, new data suggests that there is a subset of these animals that can actually respond reasonably well to therapy and consequently enjoy a near normal life.

Anytime the clinician is confronted with a hypoprotein-emic dog, the first step is to measure the serum albumin concentration as opposed to being satisfied with the serum total protein concentration. It is important not to use a human clinical pathology laboratory for this measurement as their technology may or may not detect canine albumin. Normal dogs can have measured serum albumin concentrations of 1.5 gm/dl because of methodological problems with the human technology when trying to measure canine albumin. In addition, serum albumin is a bit of a "delicate" test to run. It is clearly best to have the same veterinary laboratory measure the serum albumin each time so that one can accurately compare values run on different days.

Panhypoproteinemia is not a very reliable indicator of PLE. Dogs with PLE that initially were hyperglobulinemic may lose over half of their plasma proteins and consequently have normal serum globulin concentrations. Conversely, occasional panhypoproteinemic dogs have hepatic disease or glomerular disease as the major source of protein loss, for reasons which are not clear. Therefore, the work up for hypoalbuminemic dogs is the same regardless of whether or not they are panhypoproteinemic.

For the patient with a serum albumin < 2 gm/dl, the first step is to examine the skin for obvious lesions which could cause protein loss. Cutaneous lesions sufficient to cause such hypoalbuminemia should be very obvious. The clinician should be able to simply examine the patient and quickly ascertain whether or not the skin is the reason for the hypo-albuminemia. Following this, hepatic function testing (e.g., resting and post-prandial serum bile acid concentrations) and a urinalysis are indicated. If there is any doubt concerning the urinalysis results, then a urine protein:creatinine ratio will quantify the magnitude of urinary protein loss. Severe hypoalbuminemia (i.e., < 2 gm/dl) in a dog with diarrhea suggests a PLE; however, diarrhea (even severe diarrhea) can be due to primary hepatic disease. Many dogs and cats with PLE do not have vomiting or diarrhea, and some dogs with PLE present with only ascites. In fact, some dogs with

PLE will be fortuitously diagnosed when the dog comes in for a routine yearly wellness check and has routine blood examination.

The serum cholesterol concentration can help the clinician determine the cause of the hypoalbuminemia. Hypocholesterolemia concurrent with hypoalbuminemia suggests either PLE or hepatic insufficiency. Hypercholesterolemia occurring along with hypoalbuminemia is more suggestive of a protein-losing nephropathy.

After severe, exudative cutaneous disease, protein-losing nephropathy, and hepatic insufficiency are eliminated, then PLE is a reasonable tentative diagnosis of exclusion in patients with a serum albumin < 2.0 gm/dl. Fecal concentrations of alpha-1 protease inhibitor can be measured to try to confirm PLE if there is confusion because of concurrent hepatic or renal disease; however, this is not always an easy test to run or interpret (3, 4). The major use for this test in clinical medicine seems to be the hypoalbuminemic patient in which one strongly suspects PLE (e.g., based upon it having severe diarrhea or having hypocholesterolemia), but which also has a protein-losing nephropathy and/or hepatic disease. There are several nuances about this test, especially collecting samples that make it potentially difficult to interpret. This test is seldom needed in clinical practice.

Many dogs with PLE have relatively severe alimentary tract disease (or at least alimentary tract disease that can become life-threatening) which should be diagnosed promptly to maximize the chance for successful therapy. Hence, aggressive diagnostics are typically an appropriate recommendation. Although therapeutic trials can be chosen in place of classic diagnostic tests in many of the more common alimentary tract diseases (e.g., dietary allergy, dietary intolerance, antibiotic-responsive enteropathy, parasites), such an approach is generally ill-advised if the serum albumin concentration is less than 2.0 g/dl. This is true because it may be necessary to perform an antibiotic and/or dietary therapeutic trial for 3-6 weeks in order to ascertain if it is being effective, and a patient with severe PLE can markedly deteriorate during this time, especially if the serum albumin concentration is falling rapidly.

Any GI disease can cause PLE if it is severe enough. Many acute gastrointestinal (GI) diseases cause PLE (e.g., parvoviral enteritis); however, these diseases typically are comparatively easier to treat than the chronic GI disease causing PLE. The major causes of PLE in adult dogs tend to be intestinal lymphangiectasia, alimentary tract lymphoma (LSA), fungal infections (i.e., histoplasmosis and pythiosis), and then inflammatory bowel disease (IBD) (1). Other causes may include alimentary tract ulceration/erosion, severe disease of intestinal crypts, antibiotic-responsive enteropathy, and parasites. The major causes of PLE in juvenile dogs tend to be parastic and chronic intussusception. Cats with PLE usually have IBD or alimentary tract lymphoma. Once PLE has been diagnosed, intestinal biopsy is usually the best and more reliable means of determining the cause. Biopsy can be performed via laparotomy, laparoscopy, or endoscopy. Feeding a small, fatty meal (use canned food, not dry, and add in cream or corn oil) the night before the procedure might make it easier to diagnose lymphangiectasia on histopathology (5). Flexible endoscopy, when done by someone well trained in taking and submitting diagnostic tissue samples is usually more than adequate to obtain a solid diagnosis.

However, it is preferable to image the dog before biopsy. Radiographs and barium series are seldom useful. Abdominal ultrasound is appropriate to make sure that there are no focal infiltrates that are out of reach of the endoscope, or which might be more easily diagnosed by ultrasound-guided fine needle aspiration. Furthermore, there are ultrasonographic changes (i.e., hyperechoic streaks in the submucosa) that can be diagnostic of lymphangiectasia (and thus eliminate the need for biopsy) (6). Feeding fat the night before the ultrasound can enhance the chances of ultrasound finding dilated lymphatics in the submucosa, a finding that is considered virtually diagnostic of lymphangiectasia. (7) Lymphangiectasia can be relatively localized in one segment of the intestines. In many cases, lymphangiectasia, IBD or LSA may be obvious in the ileum but not in the duodenum. Therefore, if flexible endoscopy will be done, it is important to biopsy both the duodenum and ileum (8, 9). It is not necessary to enter the ileum with the endoscope to obtain a good tissue sample of the ileal mucosa. One can blindly pass the biopsy forceps through the ileocolic valve and typically obtain high quality mucosal biopsies of the ileum.

While histopathology is obviously the desired means of diagnosis, surgeons can sometimes make a tentative diagnosis of lymphangiectasia based upon grossly visible endoscopic findings (i.e., numerous, erratic, grossly engorged lacteals seen as large white blebs on the mucosa) (10). However, these lesions are "fragile" and apparently may be destroyed

during biopsy if the endoscopist or surgeon is not careful. Furthermore, if one biopsies the intestines and cannot find a cause of PLE, sometimes lymphangiectasia can be tentatively diagnosed by the process of eliminating all the other causes (e.g., IBD, lymphoma, parasites, intussusception, fungal infections, ulcers).

Laparotomy and laparoscopy are both proficient methods to obtain diagnostic samples, but it is surprisingly easy to procure non-diagnostic samples with both techniques. The phrase "full-thickness sample" is not synonymous with "diagnostic sample". Endoscopy does have the advantage of allowing one to visualize mucosal lesions that are "invisible" when looking at the serosa. Feeding fat the night before the procedure might make it easier to find diagnostic lesions (5). In some cases, the diagnosis can only be obtained by biopsying these focal lesions. If full-thickness biopsies are obtained in severely hypoalbuminemic animals, then serosal patch grafting will minimize the risk of suture line leakage. A nonabsorbable or a poorly absorbable suture (PDS) may also be used to lessen the likelihood of complications.

Regardless of how the samples will be taken, poor quality mucosal biopsies (e.g., primarily villi tips or substantial "squash" artifact) makes it much more difficult or even impossible to find lesions (11). If the endoscopist obtains high quality tissue samples (i.e., total length of the villi plus subvillus mucosa down to the border of the mucosa and muscularis mucosa), it typically takes about 6-7 tissue samples to have 90-99% confidence in finding lymphangiectasia. However, it can take 5-7 times as many tissue samples to have the same assurance if the clinician is obtaining poor quality tissue samples that primarily consist of villi tips.

Intestinal lymphangiectasia seems particularly common in Yorkshire terriers and Soft-Coated Wheaten terriers, but may occur in any breed (1, 12-15). Therapy for intestinal lymphangiectasia revolves around feeding an ultra-low fat diet (16). Anti-inflammatory therapy designed to alleviate the lipogranuloma formation that commonly occurs within the intestinal wall and/or mesentery is typically included. Supplementation with medium chain triglyceride oil (MCT) used to be recommended because MCT oil supposedly bypasses intestinal lymphatics thus preventing further rupturing of the lacteals. Pancreatic enzymes were often added to the diet to ensure digestion of the medium chain triglyceride oil. MCT oil is seldom used anymore, probably because appropriate dietary therapy is usually more than sufficient. Feeding homemade diets that are highly digestible and ultra-low in fat (e.g., white turkey meat plus potato or rice) or feeding commercial diets is often very helpful in these patients. Commercial low fat diets can be used very successfully, but they need to have the lowest possible fat content while at the same time having adequate calories (i.e., reducing diets are seldom optimal for treating lymphangiectasia). Such a diet can be so successful that it might occasionally be appropriate to use it as a therapeutic trial. Dogs with lymphangiectasia often show a marked increase in serum albumin concentration within 7-14 days of starting such a diet.

The importance of lipogranulomas in the intestinal wall (17) and mesentery is uncertain. However, it might be that some patients fail to respond to appropriate dietary therapy because of formation of very large or excessive numbers of lipogranulomas which completely obstruct the intestinal lymphatics so that even an ultra-low fat diet cannot prevent lacteal rupture. Therefore, once a diagnosis of lymphangiectasia is made (either by histopathology, grossly at endoscopy, or tentatively by response to an ultra-low fat diet), it seems to be appropriate to use anti-inflammatory therapy designed to prevent granuloma formation/enlargement. Prednisolone, azathioprine, and/or cyclosporine are commonly used for this purpose (18). Prednisolone (2-3 mg/kg/day) is inexpensive but has a plethora of side effects. Cyclosporine (3-6 mg/kg bid) is often helpful, but it is expensive and it is sometimes necessary to measure blood levels of the drug if the patient is not responding as desired (which adds to the cost). Not only is there a major difference between patients in how much cyclosporine they absorb (i.e., the bioavailability), but this aspect of pharmacokinetics may change dramatically as the intestine heals.

Lesions of the intestinal crypts have been recognized as being associated with PLE in dogs. There are two different lesions of the small intestinal crypts that can cause PLE (19-20). One type is characterized by crypts (usually duodenal) that are filled and somewhat distended with proteinaceous fluid and necrotic inflammatory cells. While such dilated crypts can be found in many animals (including clinically normal dogs), finding large numbers of them in multiple tissue samples is typically associated with PLE. It is not known whether or not this is a cause-and-effect relationship, or if the dilated crypts are simply a marker for some other process but are not causing the protein loss themselves. Several of these patients have responded to therapy with elemental diets,

total parenteral nutrition, prednisolone, azathioprine, and/or metronidazole. This lesion can be seen in dogs with IBD as well as lymphangiectasia (especially in Yorkshire terriers).

Chronic intussusception is a relatively important and often missed cause of PLE in juvenile animals (21). The classic history is one of acute enteritis (e.g., parvoviral enteritis) which does not resolve as expected. The patient feels somewhat better, but continues to have diarrhea, and the serum albumin concentration gradually diminishes. It can be very hard to palpate an ileo-colic intussusception; abdominal ultrasound is clearly the preferred way to diagnose intussusception. Therapy is surgical.

Although uncommon, nematodes may cause PLE in adult animals if there are large numbers of them. Whipworms and hookworms in particular may occasionally be responsible for PLE in older dogs. However, giardiasis has been reported to cause PLE in people (22).

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