PROTEIN-LOSING ENTEROPATHIES: DIAGNOSIS AND TREATMENT

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Abstract

Hypoalbuminemia is not always a bad prognostic sign in dogs with chronic GI disease. Lymphangiectasia can be treated successfully in many animals IF it is diagnosed early. However, there are several subtleties in diagnosing lymphangiectasia.

Hypoalbuminemia

When concerned with protein loss of any cause, one should measure serum albumin concentrations (NOT serum total protein concentrations). Do not use human clinical pathology laboratories as their technology typically does not detect canine albumin (meaning that they routinely report serum albumin concentrations of < 1.5 gm/dl in clinically normal dogs). If the patient has substantial hypoalbuminemia, the first step is to examine the skin for obvious lesions which can cause protein loss. Cutaneous lesions sufficient cause such hypoalbuminemia are obvious – you should be able to just look at the patient and know. Next, hepatic function testing (e.g., resting and post-prandial serum bile acid concentrations) and a urinalysis are requested. If there is any doubt on the urinalysis, then a urine protein:creatinine ratio will quantify the magnitude of urinary protein loss. Severe hypoalbuminemia (i.e., < 2 gm/dl) in an animal with diarrhea suggests a protein-losing enteropathy (PLE). If severe, exudative cutaneous disease, protein-losing nephropathy, and hepatic insufficiency are eliminated, then PLE is a reasonable tentative diagnosis in patients with a serum albumin < 2.0 gm/dl. Contrary to what the textbooks say, PLE may be associated with a low, normal or increased serum globulin concentration.

Perhaps the most important point of this discussion is that while hypoalbuminemia has repeatedly been reported to be a poor prognostic sign in patients with chronic GI disease, there may be one or more subset(s) of patients that respond well to appropriate therapy. Therefore, diagnosing PLE is not necessarily cause for despair. However, since many of these animals have severe alimentary tract disease that needs to be diagnosed promptly to maximize the chance for successful therapy, 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 become markedly worse in that time, especially if the serum albumin concentration is falling rapidly.

Causes of PLE

Any GI disease can cause PLE if it is severe enough. Many acute GI disease cause PLE (e.g., parvoviral enteritis); however, these diseases typically are comparatively easier to treat than the chronic GI disease causing PLE. Therefore, the focus in this lecture is PLE in animals with chronic GI disease. The major causes of PLE in adult dogs tend to be intestinal lymphangiectasia, inflammatory bowel disease (IBD), alimentary tract lymphoma (LSA), and fungal infections (i.e., histoplasmosis and pythiosis). Other causes 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 parasites and chronic intussusception. Cats with PLE usually have IBD or alimentary tract lymphoma.

Many dogs with PLE have hypocholesterolemia. Pets with protein-losing nephropathies usually have hypercholesterolemia, while those with hepatic insufficiency often have hypocholesterolemia. Fecal examinations for parasites are appropriate. Although parasites are an uncommon cause of PLE in adult animals, pets in select environments (e.g., confined areas where patients can reinfect themselves) may incur substantial parasitic loads.

A substantial number of dogs and cats with PLE do not have vomiting or diarrhea, just like a substantial number of dogs and cats with severe hepatic disease do not have an increased ALT or SAP. This may be especially true of dogs with primary intestinal lymphangiectasia. Fecal concentrations of alpha-1 protease inhibitor can be used as a means of confirming PLE. The major use for this test seems to be the hypoalbuminemic patient in which you suspect PLE, but which also has PLN and/or hepatic disease. However, there are several nuances about this test, especially collecting samples, that make it potentially difficult to interpret. We seldom need this test in clinical practice.

Diagnostic approach to PLE patient

Once PLE has been diagnosed, intestinal biopsy is usually the ultimate means of establishing a diagnosis. Biopsy can be done 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. Flexible endoscopy, when done by someone who is trained in how to take diagnostic tissue samples and submit them is usually more than adequate to obtain diagnostic samples. However, if endoscopy will be used to biopsy the small intestines, it is preferable to first ultrasound the abdomen 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. Radiographs and barium series are seldom as sensitive as ultrasound. If flexible endoscopy will be done, one should biopsy both the duodenum and ileum. There have been numerous cases in which lymphangiectasia, IBD or LSA were obvious in the ileum but not in the duodenum. It is not necessary to enter the ileum with the endoscope to obtain a good tissue sample of the ileal mucosa.
Laparotomy and laparoscopy are good means of obtaining diagnostic samples, but it is surprisingly easy to procure non-diagnostic samples with these techniques (i.e., “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. 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) should also be used.

Intestinal lymphangiectasia seems particularly common in Yorkshire terriers and Soft-Coated Wheaten terriers, but may occur in any breed. Sometimes these dogs have distinct ultrasonographic findings: “steaks” in the mucosa that represent dilated lymphatics. While histopathology is obviously the desired means of diagnosis, one can sometimes make a definitive diagnosis based upon gross endoscopic findings (i.e., numerous, erratic, grossly engorged lacteals seen as large white blebs on the mucosa). These lesions are “fragile” and apparently may be destroyed by biopsying them (both endoscopically and surgically) if the endoscopist or surgeon is not careful. It is important to note that lymphangiectasia can be a relatively localized disease in the intestines, being present in only the ileum or only the jejunum or only the duodenum; therefore, it is important to biopsy as much of the intestinal tract as possible. Furthermore, if one biopsies the intestines and cannot find a cause of PLE, sometimes lymphangiectasia can be diagnosed by default (i.e., by eliminating IBD, lymphoma, parasites, intussusception, fungal infections, etc).

Diagnosis by means of endoscopic biopsy is certainly possible, but recent work has shown that poor quality biopsies (e.g., primarily villus tips) makes is much more difficult to find the lesions. If one is taking 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 3-6 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 you are obtaining poor quality tissue samples that primarily consist of villus tips.

Therapy for intestinal lymphangiectasia revolves around an ultra-low fat diet, preferably with anti-inflammatory therapy designed to alleviate the lipogranuloma formation that commonly occurs within the intestinal wall and/or mesentery. 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. 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 important of lipogranulomas in the intestinal wall and mesentery is uncertain. However, it is hypothesized that some patients fail to respond to appropriate dietary therapy because of formation of very large or excessive numbers of lipogranulomas that so completely obstruct the intestinal lymphatics that even an ultra-low fat diet cannot prevent lacteal rupture. Therefore, once a diagnosis of lymphangiectasia is made (either by...
histology, grossly at endoscopy, or tentatively by response to an ultra-low fat diet), it may be appropriate to use anti-inflammatory therapy designed to prevent granuloma formation/enlargement. Prednisolone, azathioprine, and/or cyclosporin are commonly used for this purpose.

It is exceedingly difficult to increase the serum albumin concentration by transfusing PLE patients with plasma because so much of the albumin is quickly lost out the gut. You would probably have to give at least two units of plasma to a 15 lb dog in order to raise the serum albumin from 1.0 gm/dl to 1.8 gm/dl, and sometimes you would have to give 3 or 4 units. If it is critical to raise the plasma oncotic pressure, then administering hetastarch may be preferred because it costs less than plasma and it stays in the intravascular compartment longer than albumin.

**Selected reading:**