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Protein-losing enteropathies

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Protein-losing enteropathy (PLE) refers to a syndrome in which intestinal disease is causing nonselective protein loss such that hypoalbuminemia results. A more strict definition would include any intestinal disease in which there is greater than normal loss of protein from the intestinal tract, but we only recognize those cases in which sufficient protein loss occurs that the liver's ability to produce albumin is exceeded and we detect hypoalbuminemia.

Almost every intestinal disease has been reported to cause PLE in some species, and there are several mechanisms by which PLE occurs. Inflammation, ulceration, erosion, neoplastic disruption of the mucosa, rupture of lymphatics into the lumen, and probably also damage to the tight junctions between epithelial cells may result in gastrointestinal (GI) protein loss [1]. Reduced protein intake or absorption, although capable of making hypoalbuminemia in patients with PLE worse, is almost never the sole or major cause of serum albumin concentrations less than 2.0 g/dL. Exceptions to this statement might include neonates or animals fed extremely low-protein diets for substantial periods.

Diagnostic approach

Clinical signs in PLE patients may be suggestive of protein loss (ie, ascites), or they may be vague and nonspecific (eg, weight loss). Diarrhea is not consistently found in PLE patients; many have normal stools without vomiting or anorexia. Some sequelae to PLE (eg, thromboembolic disease) can be life threatening but may not be something that most people associate with intestinal disease. Serum albumin should be measured in every animal

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with severe or chronic GI signs, ascites, and suspected thromboembolic disease.

Because diagnosing PLE begins with detecting hypoalbuminemia, one must always measure the serum albumin concentration as opposed to just the total protein concentration. There are two mistakes commonly made when assessing serum proteins in dogs. First, although PLE is classically associated with panhypoproteinemia, many dogs with PLE do not have hypoglobulinemia. There are numerous reasons for excessive globulin production in dogs (eg, ehrlichiosis, heartworm disease, chronic skin disease); we often find PLE dogs with normal serum globulin concentrations. Second, the methods used by some human clinical pathology laboratories do not measure canine albumin. Dogs with normal serum albumin concentrations (eg, 3.0 g/dL) can have results assayed as less than 1.0 g/dL if the wrong methodology is used.

Once hypoalbuminemia has been documented, the cause must be identified. The main causes of a serum albumin concentration less than 2.0 g/dL are PLE, protein-losing nephropathy (PLN), hepatic insufficiency (HI), and cutaneous losses. Care must be taken in distinguishing these causes. Hypoalbuminemic dogs with signs of GI disease (eg, vomiting, diarrhea) may have PLN or HI. It is easiest to eliminate cutaneous losses (by examining the skin) and PLN (urinalysis $\pm$ protein:creatinine ratio) initially. Any animal with an active sediment can have a high protein:creatinine ratio even if it has no glomerular disease, so lower urinary tract disease should be ruled out initially. Because glucocorticoids can cause proteinuria, a urinalysis should also be performed before initiation of steroid therapy [2]. Next, serum bile acid measurements are used to look for HI. Once these three causes of hypoalbuminemia are eliminated, PLE is diagnosed by exclusion.

Distinguishing PLE from HI can be difficult. Hypoalbuminemia, hypocholesterolemia, and decreased blood urea nitrogen (BUN) can all be associated with either PLE or HI. Furthermore, many patients with severe hepatic disease do not have hyperbilirubinemia or marked hepatic enzyme elevations. Normal pre- and postprandial serum bile acid concentrations eliminate HI as a cause of major hypoalbuminemia in most cases. Increased serum bile acid concentrations are not as easy to evaluate, however. Nonhepatic diseases (including GI disease) cause mild to moderate (and sometimes major) increases of serum bile acid concentrations. Concurrent collection of hepatic and GI biopsies is occasionally required to differentiate primary liver diseases from reactive hepatopathies.

Measuring fecal α_1-proteinase inhibitor (α_1-PI) concentrations is sometimes needed to confirm the presence or absence of PLE in difficult cases (eg, PLE patients with concurrent PLN or HI). α_1-PI is a normal inhibitor of proteases (eg, trypsin) and is approximately the same size as albumin [3]. Whenever albumin is lost into the GI tract, α_1-PI accompanies it and is excreted in the feces undegraded, thus acting as a marker of PLE [3]. There is only one laboratory that currently offers the species-specific enzyme-linked immunoassay for canine α_1-PI (Gastrointestinal Laboratory, Texas A&M

University, College Station, TX) [3]. Three separate voided fecal specimens (it is critical that feces not be removed from the rectum via digital means) are collected into volume-calibrated cups available from the laboratory [4]. Samples should be immediately frozen after collection and shipped on ice overnight for optimal results, because the fecal α_1-PI concentration has been found to be only 66% of prestorage concentration when kept at room temperature for 72 hours [3].

Because patients with PLE can become quite ill as the serum albumin concentration decreases, therapeutic trials, which are often reasonable with non-PLE GI diseases, are inappropriate if PLE is suspected. Prompt diagnosis of the cause and specific therapeutic measures are preferred. GI biopsies are required for a definitive diagnosis in most cases of PLE. Laparotomy allows full-thickness GI biopsies plus wedge liver biopsies when indicated, but recovery may be complicated in dogs with PLE. When taking surgical intestinal biopsies from severely hypoalbuminemic dogs, serosal patch grafting may give the clinician additional confidence that dehiscence is unlikely. Intestinal and hepatic biopsy may be accomplished via laparoscopy, which is less invasive and less prone to complications than laparotomy. It is best to avoid removing the abdominal fluid during the biopsy technique. When fluid is removed, the albumin in the fluid is also removed, ultimately decreasing the total body albumin stores; thus, ascites reforms even faster as the serum albumin concentration is reduced even further.

Flexible endoscopic biopsies are most desirable initially unless abdominal ultrasound reveals a lesion that cannot be reached with a flexible scope. Endoscopy is associated with a shorter anesthesia time and fewer potential complications than surgery; in addition, it allows one to obtain multiple diagnostic samples and facilitates identification of mucosal lesions not detectable from the serosal surface. The authors prefer to start with several high-quality endoscopic biopsies from the stomach, duodenum, ileum, and colon in patients with suspected PLE.

Clinical presentation with protein-losing enteropathy

PLE may occur in young or old animals. Cats seemingly develop PLE less often than dogs. Different breeds of dogs affected with PLE between 1987 and 2002 at Texas A&M Veterinary Hospital were surveyed to determine which dogs were predisposed. Medical records coded with the diagnosis of PLE, lymphangiectasia, inflammatory bowel disease (IBD; including lymphocytic, plasmacytic, and eosinophilic forms), GI lymphoma, GI ulcer, intussusception, and histoplasmosis were retrospectively reviewed, because these diagnoses represent the most common forms of PLE in our hospital. Dogs were considered to have PLE if they were hypoalbuminemic (albumin concentration $<$ 2.4 g/dL); had no evidence of significant proteinuria (negative dipstick if urine specific gravity [USG] $<$ 1.020, 1+ or less on

dipstick if USG $\geq$1.020 or urine protein:creatinine ratio < 1.0); had no reported cutaneous losses; and had no evidence of significant hepatic dysfunction on biochemical profile, serum bile acid testing, or hepatic biopsy. HI could not be ruled out in all dogs, because serum bile acid concentrations and hepatic biopsies were not always performed. Proteinuric animals were included only if PLE was confirmed on fecal α_1-PI concentrations and GI biopsies supported a diagnosis of PLE. Univariate analysis of breed for PLE comparing dogs with PLE with the overall hospital population during the same period revealed that Shar Peis (odds ratio [OR] = 10.4) and Rottweilers (OR = 2.4) were at increased risk for PLE ($P < 0.05$), as shown in Table 1. Breed predisposition for PLE in Yorkshire Terriers (OR = 4.3) and Soft-Coated Wheaton Terriers (OR = 24.9) was similar to that previously reported, as described below.

Yorkshire Terriers

When compared with one hospital population, Yorkshire Terriers were found to have an OR of 10.1 for development of PLE, and a similar predisposition was noted in our hospital. Affected dogs commonly had lymphangiectasia and lymphocytic plasmacytic enteritis and were more likely than other breeds to be hypocalcemic and hypomagnesemic. Although malabsorption and GI loss of calcium, magnesium, and vitamin D as well as inadequate parathyroid hormone production are suggested as possible causes for the breed-related phenomenon, the exact pathogenesis is unknown [5].

Soft-Coated Wheaton Terriers

A heritable form of PLE with or without concurrent PLN has been well described in the Soft-Coated Wheaton Terrier. The disorder is most common in middle-aged female dogs, and 10% to 15% of the breed population is estimated to be affected. Dogs with PLE have similar histopathologic changes, including mononuclear inflammation, lymphangiectasia, and lipogranulomatous lymphangitis [6]. An underlying hypersensitivity or immunoregulatory disorder is suspected, although the exact pathogenesis remains unknown [7].

Chinese Shar Peis

The authors have noted that Chinese Shar Peis commonly develop inflammatory intestinal infiltrates associated with PLE. Renal amyloidosis is also common in the breed, so hypoalbuminemic Shar Peis cannot be presumptively diagnosed as having PLE.

Basenjis

A predisposition for the development of chronic diarrhea, hyperglobulinemia, and an intense lymphocytic-plasmacytic GI infiltrate (sometimes

Table 1
Results of univariate analysis of breed for development of protein-losing enteropathy and hypoalbuminemia (serum albumin < 2.4 g/dL) (1987–2002)

Variable	No. dogs affected	Odds ratio	95% confidence interval	*P* value
All forms of nonproteinuric PLE[a]	138			
Rottweiler	9	2.4	1.2–4.6	0.011
Chinese Shar Pei	8	10.4	5.1–21.4	< 0.001
Yorkshire Terrier	10	4.3	2.3–8.2	< 0.001
All forms of PLE[b]	201			
Chinese Shar Pei	9	7.9	4.0–15.6	< 0.001
Soft-Coated Wheaton Terrier	3	24.9	7.6–81.5	< 0.001
Yorkshire Terrier	14	4.1	2.4–7.1	< 0.001
Inflammatory bowel disease	48			
German Shepherd	5	3.6	1.4–9.0	0.004
Mixed breed	4	0.3	0.1–0.9	0.028
Chinese Shar Pei	5	19.5	7.7–49.5	< 0.001
Uncharacterized PLE[c]	38			
Yorkshire Terrier	8	14.7	6.7–32.1	< 0.001
Lymphangiectasia	32			
Poodle	4	4.5	1.6–12.9	0.002
Chinese Shar Pei	3	17.2	5.2–56.8	< 0.001
Yorkshire Terrier	3	5.7	1.7–18.6	0.001
GI ulcers	30			
Dachshund	4	4.5	1.6–13.0	0.002
Mixed breed	12	2.4	1.2–5.1	0.010
Histoplasmosis	29			
Schnauzer	4	6.9	2.4–19.8	< 0.001
Intussusception	17			
Labrador Retriever	7	7.7	2.9–20.2	< 0.001

Abbreviations: GI, gastrointestinal; PLE, protein-losing enteropathy.

[a] Includes all nonproteinuric hypoalbuminemic dogs coded with a diagnosis of inflammatory bowel disease, PLE, lymphangiectasia, GI ulcer, histoplasmosis, GI lymphoma, and intussusception. Dogs with liver disease excluded in all groups except for histoplasmosis. Breeds with fewer than 3 dogs were excluded from analysis.

[b] Same as PLE group above, but proteinuric dogs not excluded.

[c] Hypoalbuminemia confirmed as a result of PLE, but no histopathologic diagnosis obtained.

termed *immunoproliferative enteropathy*) is reported in the Basenji breed [8]. We see few Basenjis at our hospital and only had one Basenji with PLE in the past 15 years; therefore, this breed failed to achieve statistical significance for predisposition (OR = 4.16, $P = 0.13$). Lesions in Basenjis tend to be more severe in symptomatic dogs but can also be found in asymptomatic dogs. Affected dogs may develop hypoalbuminemia with hyperglobulinemia, severe weight loss, and death 0 to 3 years after onset of diarrhea. Although prednisone, oral broad-spectrum antibiotics, and dietary therapy often reduce clinical signs, the disease is progressive in some dogs [8].

Miscellaneous breeds

A breed predisposition for PLE and lymphangiectasia is reported in the Lundehund [9,10]. German Shepherds seem to be at increased risk for IBD, which may be associated with PLE when severe [11]. Dachshunds were at increased risk for severe GI ulceration in our hospital population, with affected dogs commonly receiving corticosteroids and nonsteroidal anti-inflammatory drugs for pain associated with intervertebral disk disease. Rottweilers were affected with several different forms of PLE, including IBD (three dogs), lymphangiectasia (two dogs), GI ulcers (two dogs), uncharacterized PLE (two dogs), and GI lymphoma (one dog).

Presenting clinical signs

Clinical signs and severity of PLE may vary depending on the severity of underlying disease, the segment of the GI tract affected, and the duration of disease. The clinical findings in 134 dogs with PLE derived from six case series are presented in Table 2 [5,6,8,9,12,13]. These data may not reflect the prevalence of these signs in the general population in that the dogs cited come largely from a referral population and lymphangiectasia, Basenjis, and Soft-Coated Wheaton Terriers are overrepresented. The data do reflect the variable presentation of dogs with PLE, however.

GI tract–associated clinical signs are the most common presenting problems in dogs with PLE. Chronic, intermittent, small bowel diarrhea occurs in most affected dogs, and intermittent vomiting, anorexia, and weight loss commonly accompany the diarrhea. It is noteworthy that some dogs with PLE do not have diarrhea, weight loss, or vomiting, however. Ascites and edema generally develop when the serum albumin concentration is between 1.0 g/dL and 2.0 g/dL [14]. In the authors' experience, third space fluid

Table 2
Clinical findings in 134 dogs with protein-losing enteropathy

Clinical finding	Percentage of PLE dogs affected
Diarrhea	96
Vomiting	56
Weight loss	> 52
Ascites/edema/pleural effusion	44
Ascites	41
Pleural effusion	5
Peripheral edema	7
Thromboembolic disease	10
Polyuria/polydipsia	5
Seizure/twitching	4

Abbreviation: PLE, protein-losing enteropathy.
Data from Refs. [5,6,8,9,12,13].

accumulation usually does not occur until the serum albumin concentration is less than 1.6 g/dL, and some patients with serum albumin concentrations of 1.3 g/dL do not have ascites or edema. Abdominal distention attributable to ascites is the most common clinical manifestation of severe hypoalbuminemia, although pure transudate formation may also occur in the pleural space and result in tachypnea, dull lung sounds, and dyspnea.

Occasionally, the PLE patient may be presented for dyspnea, which can have a multifactorial cause. Possible causes include hydrothorax, pulmonary edema, and pulmonary thromboembolic disease. Enteric loss of antithrombin III may induce a hypercoagulable state, and pulmonary, distal aortic, and hepatic thromboemboli have been reported in dogs with PLE [6,14]. Neurologic signs (eg, twitching, seizures) may occur secondary to thromboembolic disease, cerebral edema, or hypocalcemia. Ionized calcium concentrations more accurately reflect biologically active concentrations than total serum calcium concentrations and should be measured in PLE patients.

Specific causes of protein-losing enteropathy

Although almost any severe GI disease can result in protein loss, some diseases are more commonly associated with PLE than others. PLE as a result of chronic disease is usually of more concern than PLE as a result of acute disease, because the acute diseases (eg, parvovirus enteritis) often are self-limiting if the patient can be supported long enough.

Lymphangiectasia

Intestinal lymphangiectasia (IL) is dilatation of intestinal lymphatics and is classically depicted in Fig. 1, which demonstrates lacteal dilation in the villi. The dilation can also be found in the deeper portions of the mucosa or between the mucosa and submucosa (Fig. 2). IL can be a primary disorder or acquired as a result of lymphatic blockage by a mass lesion (eg, neoplasia, inflammatory infiltrates) or elevated venous pressure (eg, congestive heart failure, portal hypertension) [10,15]. IL results in extravasation of protein-rich lymph into the intestinal tract through the rupture of lacteals, increased paracellular permeability, enhanced hydrostatic tissue pressure, and decreased absorption through a damaged or malformed intestinal mucosal layer [10].

IL is a disease of dogs and has not been reported in cats. Yorkshire Terriers are overrepresented in case series and breed analyses [5,12]. Clinical signs can include diarrhea and weight loss, but some patients have ascites as the primary presenting complaint. Lymphopenia and hypocholesterolemia may be associated with IL, although this finding is inconsistent [12].

Diagnosing IL depends on (1) documenting hypoalbuminemia caused by PLE, (2) eliminating an underlying cause for IL, and (3) finding lesions of IL. Seeing many expanded white villi at endoscopy (Fig. 3) is strongly suggestive

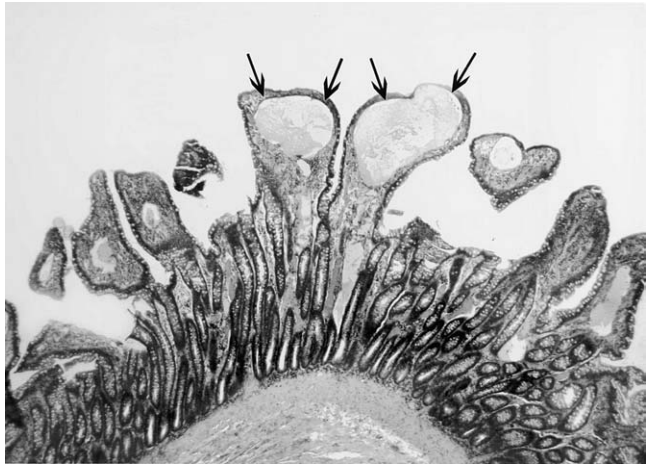

Fig. 1. Photomicrograph of intestinal mucosa with obvious lymphangiectasia as evidenced by dilated lacteals in the tips of the villi (*arrows*).

of IL. Feeding a small meal rich in corn oil or cream the night before endoscopy seems to make the diseased lymphatics more apparent grossly. Normal dogs also have their lacteals accentuated, but their lacteals are of a fine and more uniform texture. Finding large globular accumulations of chyle over duodenal lymphoid follicles is also normal. Feeding fat the night before biopsy can make lymphangiectasia more evident histopathologically (Fig. 4). Chylous fluid can sometimes be seen in the intestinal lumen as

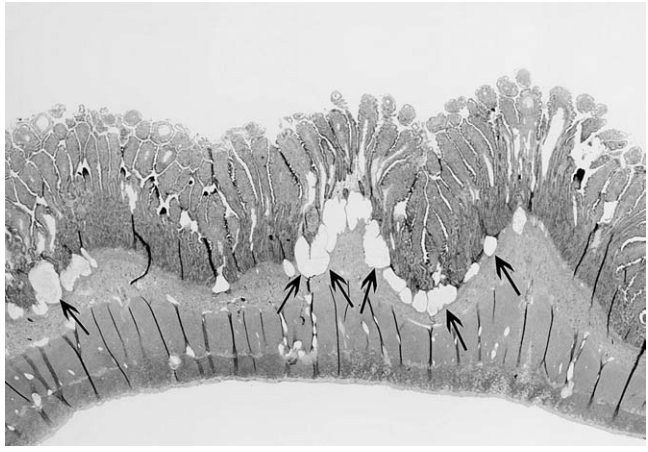

Fig. 2. Photomicrograph of intestine showing lymphangiectasia as evidenced by dilated lymphatics located between the mucosa and the muscularis mucosa (*arrows*). These lymphatics would almost certainly be missed if an endoscopic biopsy were taken of this area. (*From* Willard MD, Helman JM, Fradkin JM, et al. Intestinal crypt lesions associated with protein-losing enteropathy in the dog. J Vet Intern Med 2000;13(3):298–307; with permission.)

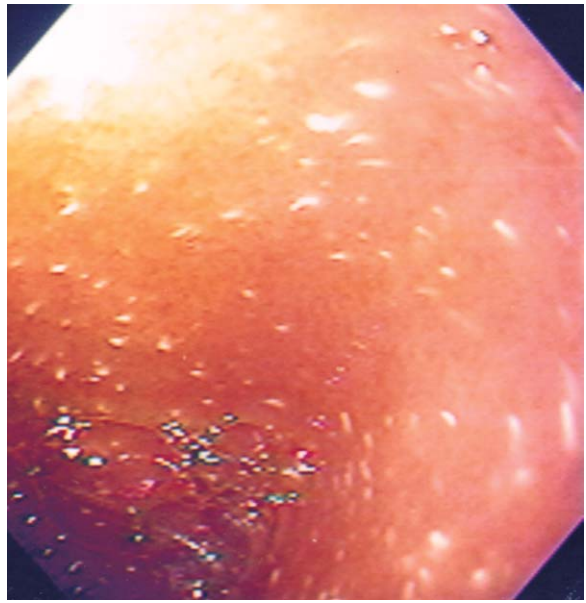

Fig. 3. Endoscopic view of duodenal mucosa of a dog with lymphangiectasia. The white "dots" correspond to lacteals that are dilated and filled with chyle (see Fig. 1).

biopsies are performed (Fig. 5), probably because biopsy ruptures the dilated lymphatics in the mucosa, allowing chyle to enter the lumen. IL may be a localized or at least a regionalized disease. The authors have noted a few cases in which the histopathologic lesions of IL were more apparent in ileal biopsies than in duodenal biopsies (Fig. 6). This focal distribution is consistent with what has been reported in human beings [16].

Abnormalities apparent at exploratory laparotomy may include small intestinal thickening, lymphatic dilation, and lymphadenopathy [12]. Some dogs with IL have obvious lipogranulomas recognized as variably sized yellow-white nodules, often located at the point of mesenteric attachment to the small intestine or colon [17]. These lesions are thought to be secondary to regional granulomatous inflammation in response to stagnated chyle or leakage of ruptured lymphatics, and they should not be confused with metastatic neoplasia [17].

There are potential problems in the diagnosis of IL. First, there is the possibility that "squeezing" the mucosa with flexible biopsy forceps may cause collapse of the dilated lacteals during biopsy and artifactually eliminate the lesion. Second, some patients with IL seemingly have dilated lymphatics that are primarily found between the mucosa and submucosa, which could be essentially impossible to find endoscopically (see Fig. 2). Surgery may therefore be required to find IL in some patients, although endoscopy is a good first choice in most patients. Third, IL has been found in people

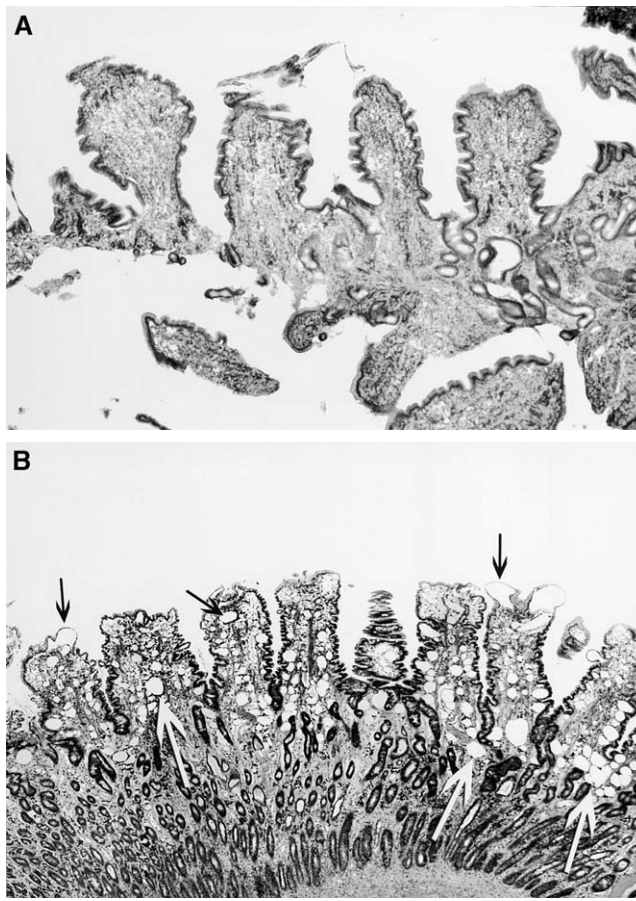

Fig. 4. (*A*) Photomicrograph of duodenal mucosa. This represents a poor-quality tissue specimen that does not include the full thickness of the duodenal mucosa. Note that there is no obvious dilatation of lacteals in the villi. (*B*) Photomicrograph of duodenal mucosa from the same dog. This tissue specimen was obtained after the dog was fed a high-fat meal the night before biopsy. Note the numerous dilated lymphatics seen throughout the villi (*black arrows*) and deeper lamina propria (*white arrows*). Compare this figure with Fig. 4A; the diagnosis of lymphangiectasia would be impossible in the latter but is obvious in this figure.

without PLE. This disparity possibly occurs because there are only a few dilated lymphatics, and the remaining intestines make up for the protein loss occurring there. We believe we have seen a similar situation in a few dogs.

Management of IL is focused on reducing absorption of fat by reducing the fat content in the diet. A home-cooked dietary trial is often initially indicated because it allows for a highly palatable and ultra–low-fat diet. Feeding one part of white turkey breast without skin plus two parts of white potato without skin (all boiled, baked, or microwave cooked) is often successful. One may produce a completely balanced diet (Table 3) if the

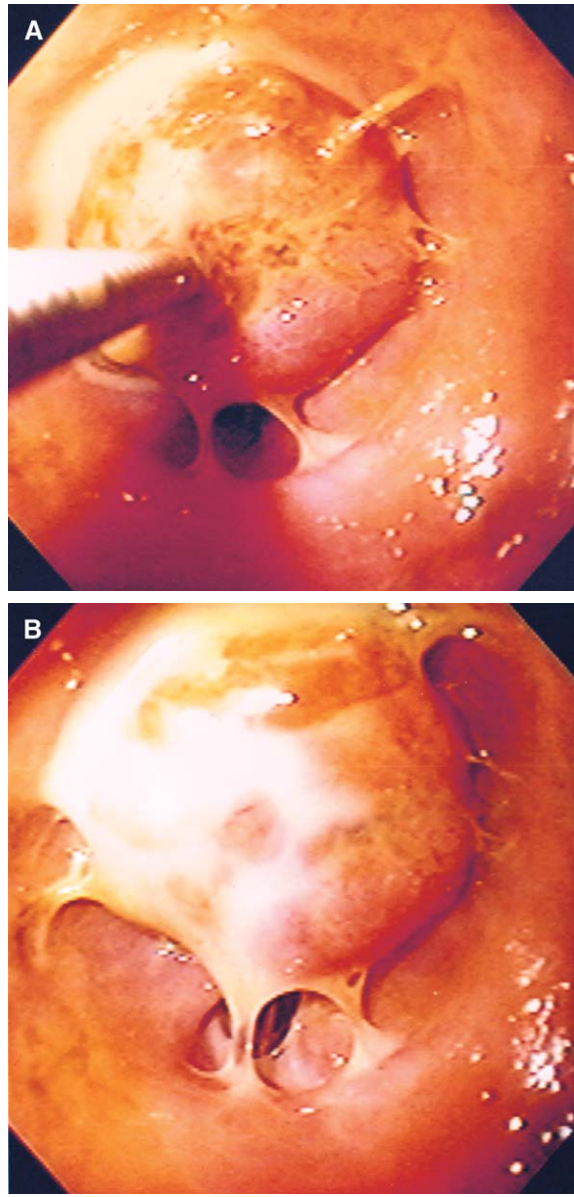

Fig. 5. (*A*) Endoscopic view of a biopsy instrument being passed through the ileocolic valve of a dog to biopsy the ileal mucosa. (*B*) Note the copious amounts of white fluid (chyle) that result, showing that dilated lymphatics filled with chyle were disrupted by the biopsy.

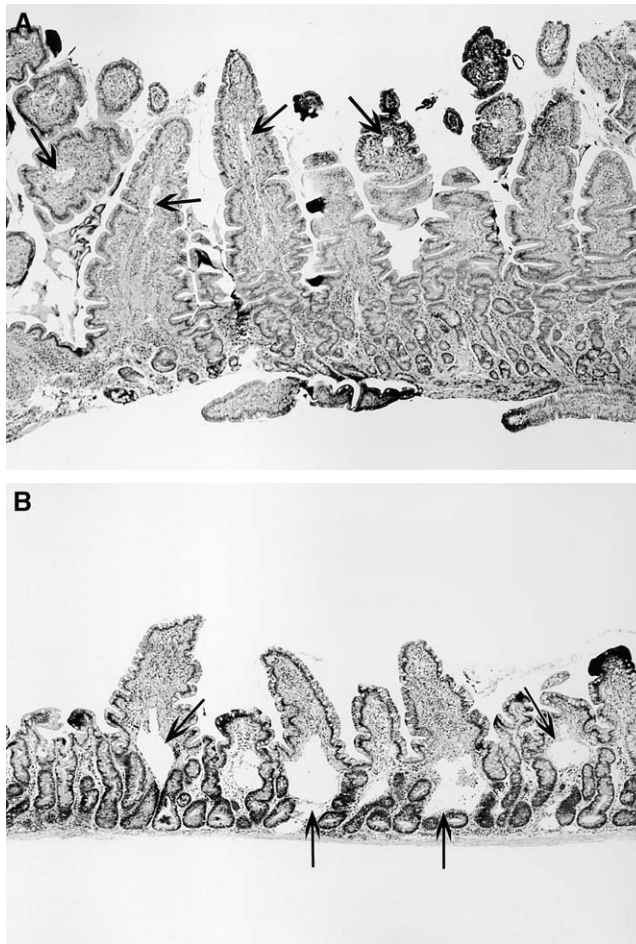

Fig. 6. (*A*) Photomicrograph of duodenal mucosa from a Yorkshire Terrier with PLE as a result of lymphangiectasia. Lacteals can be seen (*arrows*), but they are so small as to be consistent with what could be seen in any normal dog. (*B*) Photomicrograph of ileal mucosa from the same Yorkshire Terrier showing marked lymphangiectasia (*arrows*) that is clearly evident and significant. This is from the same dog represented in Fig. 5.

homemade diet must be used indefinitely. Medium chain triglyceride (MCT) oil is often mentioned in connection with IL [18]. Most dogs dislike its taste, however, and it is seldom needed. Adjunct corticosteroid therapy is beneficial in some dogs, possibly because it decreases lipogranulomas that may be occluding lymphatics [17]. Biopsies have been reported to reveal variably increased numbers of lymphocytes, plasma cells, and eosinophils in the lamina propria; however, it is uncertain if this inflammation represents a primary or secondary process and if the inflammation present is significant enough to justify glucocorticoid therapy [12].

Table 3
Sample balanced ultra–low-fat home-cooked diet for dogs

Ingredient	Amount
Boiled potatoes, no skin	1.5 cups
Enriched egg noodles, cooked	2 cups
Nonfat cottage cheese	0.5 cup
Cooked egg white from four eggs	0.5 cup
Corn oil	1 teaspoon
Lite salt	0.5 teaspoon
Dicalcium phosphate	0.5 teaspoon
Calcium carbonate (containing 600 mg of calcium)	1 tablet
Pet Tabs Plus (Pfizer, New York, NY) or equivalent	1 tablet
Centrum Adult (Wyeth Consumer Healthcare Products, Madison, NJ) or equivalent	1/2 tablet
Zinc gluconate, 50 mg	1/2 tablet
Selenium, 100 μg	1/2 tablet
GNC choline bitartrate, 250 mg (General Nutrition Corporation, Pittsburg, PA)	1/2 tablet

Cook the potatoes, noodles, and egg whites. Crush the tablets used in the recipe, and combine all ingredients. Mix thoroughly. Unused portions should be refrigerated and discarded if not fed within 7 days. This recipe makes about 3.5 cups of food containing 190 kcal per cup of food.

(Courtesy of William J. Burkholder, DVM, PhD.)

The prognosis for uncomplicated IL is usually good with therapy. Occasionally, dogs experience complications during biopsy collection (eg, dehiscence, pulmonary edema associated with fluid therapy), thromboembolic disease, or recurrence of hypoalbuminemia, particularly with poor dietary compliance. For unexplained reasons, some patients do not respond well to therapy, possibly because the IL is secondary to an undiscovered (and therefore untreated) disease process.

Inflammatory bowel disease

For the purposes of this review, IBD is defined as idiopathic inflammation of the intestines. Our understanding of this syndrome is still evolving; however, it seems apparent that (1) the inflammation is often denoted by increased numbers of lymphocytes, plasma cells, eosinophils, neutrophils, or some combination of these cell types in the lamina propria; (2) it is usually the more severe cases of IBD that are associated with PLE; and (3) both dogs and cats develop IBD, although PLE caused by IBD seems to be more common in dogs than in cats [11,19,20]. The cause(s) of these inflammatory infiltrates are unknown, although bacterial or food antigens are suspected, possibly associated with defects in the tolerance mechanisms of gut-associated lymphoid tissue [11].

Because the focus of this article is PLE, the controversies about the cause(s), diagnosis, and treatment of IBD are not addressed in depth. Nevertheless, we would like to review briefly two key points about correct

diagnosis of IBD. First, it just as important to eliminate known causes of intestinal disease (eg, bacterial and dietary causes) as it is to biopsy the intestines. Second, many endoscopic intestinal biopsies are done poorly, making the pathologist's job harder than it already is. There is good evidence of significant inconsistency between pathologists in how the same sections of intestine are described (ie, normal, mildly infiltrated, moderately infiltrated, severely infiltrated), and well-oriented and high-quality biopsies may help to minimize difficulty with biopsy interpretation [21].

IBD as a sole disease must be severe to cause PLE. Therefore, aggressive anti-inflammatory drugs (ie, glucocorticoids, metronidazole, azathioprine or chlorambucil) are typically employed in these patients. Appropriate nutritional therapy is probably at least as important as, if not more important than, anti-inflammatory therapy. Increased mucosal permeability may be an important factor perpetuating inflammation in IBD patients, and dietary proteins are among the most immunogenic antigens to which the gut is exposed [18]. Controlling gut exposure to antigenic load therefore seems appropriate. Large doses of catabolic corticosteroids are also typically used and may increase the need for protein intake in the patient that is already hypoalbuminemic [22].

Total parenteral nutrition (TPN) restores positive nitrogen balance, helps to prevent excessive catabolism of body protein stores, and helps to restore impaired immunocompetence in patients with IBD. TPN has a relatively high daily cost and potentially serious complications (eg, catheter-induced sepsis, electrolyte abnormalities, fluid overload), however [23]. TPN has been beneficial in some of our more severely affected PLE patients, and we prefer to use it in emaciated patients that are vomiting or have profuse diarrhea.

Enteral nutrition using an oligomeric elemental diet (Table 4) has been important in several of our cases. Such diets are easily absorbed by diseased intestine, cause less mucosal inflammation in intestines with increased permeability, and may attenuate fluid and albumin loss into the intestinal lumen [24]. Elemental diets seem to hasten clinical recovery (as seen by body weight gain and increased serum albumin concentrations) and minimize villous atrophy at a lesser daily cost than TPN; in addition, they do not have

Table 4
Sample elemental total enteral diet supplemented with amino acids for the severely hypoalbuminemic dog

Ingredient	Amount
Vivonex TEN powder (Novartis, Fremont, MI)	1 package
8.5% Aminosyn with electrolytes (Abbott Laboratories, Abbott Park, IL)	250 mL
Water	350 mL
Pet-Tinic (Pfizer, New York, NY) or equivalent	5 mL

Mix ingredients in a blender, and store unused portions in a refrigerator. Each milliliter of this liquid diet has 0.6 kcal.

as many potentially serious side effects, do not require as much biochemical monitoring, and can be administered at home. Theoretically, these diets should augment the anti-inflammatory effects of corticosteroids. Preformulated human products are typically supplemented with additional amino acids. The solutions can be flavored with canine vitamin supplements to enhance palatability, and many patients readily drink them. If the patient refuses to drink the solution, it may be fed through a nasoesophageal or esophagostomy feeding tube.

Gastrointestinal neoplasia

Lymphoma

GI lymphoma shares several clinical and histopathologic features with severe IBD and results in hypoproteinemia and hypoalbuminemia in approximately 75% of affected dogs and 25% of affected cats [25,26]. Moderate to severe lymphocytic-plasmacytic inflammation is reported to occur frequently adjacent to, or occasionally distant from, neoplastic foci [25]. Neoplastic tissue usually originates in multiple sites in the mucosa or submucosa of the stomach, small intestine, or colon and may be noted in distant sites (eg, liver) in multicentric lymphoma [25]. Superficial biopsies may only retrieve reactive tissue overlying neoplastic infiltration, and submucosa may be important for diagnosis [25]. Immunocytochemical staining to establish whether mucosal lymphocytes are homogenous or heterogeneous may help in selected cases. Individuals diagnosed with GI lymphoma may have been previously diagnosed as having IBD, which could be the result of (1) having both diseases present and having a nonuniform distribution of lymphoma throughout the intestines, (2) an initial misdiagnosis (ie, very well-differentiated feline intestinal lymphoma can be almost indistinguishable from severe IBD), or (3) the fact that IBD may be a prelymphomatous change in some animals (much discussed but seldom proven) [8,25].

Aged male dogs seem predisposed to GI lymphoma and commonly exhibit progressive intractable clinical signs (eg, vomiting, diarrhea, hematochezia) [25]. Response to therapy with prednisone and combined chemotherapy protocols is generally poor and can cause GI ulceration and perforation [25]. Cats with GI lymphoma may exhibit milder signs (eg, anorexia, weight loss) [26]. Cats treated with combined protocols, including vincristine, cyclophosphamide, prednisone, and (more recently) doxorubicin, are frequently poorly responsive, with a reported median survival of 50 to 201 days [26,27]. Cats with well-differentiated lymphocytic lymphoma may achieve durable remission (median of 16 months) with oral prednisone and chlorambucil therapy, however [28].

Adenocarcinoma and other gastrointestinal tumors

Many types of GI neoplasia cause PLE by a number of mechanisms (eg, blood loss from ulcerated mucosa). Lesions may be focal and missed with

endoscopy if the lesion is out of reach of the endoscope (eg, in the jejunum). Older animals with PLE should be evaluated for focal or metastatic lesions via ultrasound.

Histoplasmosis

Histoplasma capsulatum, a saprophytic fungus widely distributed in the midwestern and southern United States, can affect the colon, causing hypoalbuminemia, fever, and weight loss in dogs of all ages [29,30]. In our experience, cats rarely have primary GI signs with histoplasmosis. HI causing decreased albumin synthesis and glomerulonephritis causing proteinuria may worsen the hypoalbuminemia in affected dogs [29].

Histoplasmosis is frequently diagnosed cytopathologically from rectal scrapings. Yeasts are typically seen in colonic macrophages (Fig. 7) but may rarely be found in circulating white blood cells (WBCs), lymph node, bone marrow, or hepatic or splenic macrophages. Cytopathology, histopathology, and fungal culture are superior to serology, which has poor sensitivity and specificity [31]. Multiple cytopathology or biopsy samples may be required, because the organism may not be uniformly distributed.

Treatment using ketoconazole in affected dogs was disappointing in reported cases [29]. Amphotericin B therapy resolved clinical signs in five of seven treated dogs, but disease relapse was noted in four cases 6 to 15 months after therapy [30]. Optimal therapy for histoplasmosis and required duration have not been described, and recent reports using newer therapeutic agents are largely lacking in the literature. The authors have had success with oral itraconazole therapy used for at least 6 months in dogs without severe

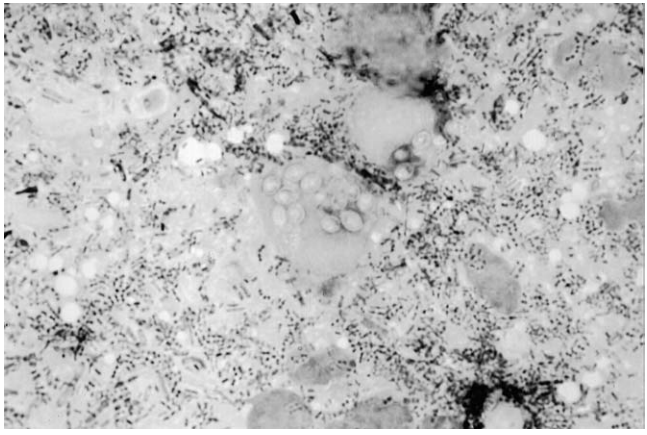

Fig. 7. Photomicrograph of a rectal scraping from a dog with colonic histoplasmosis. Note the organisms in a macrophage. (*From* Nelson RW, Couto CG. Small animal internal medicine. 2nd edition. St. Louis: Mosby; 1998. p. 442; with permission.)

disseminated disease. Our preliminary experiences with liposomal amphotericin B therapy for disseminated cases have been variable.

Gastrointestinal ulceration or erosion

GI ulcerative or erosive disease occurs when the mucosal barrier fails and the submucosa or deeper tissues are exposed to the luminal contents. Ulcers may result from increased acid production (eg, hypersecretory states) or from weakened mucosal defenses. In dogs, one or multiple predisposing conditions can usually be identified [32]. Nonsteroidal anti-inflammatory drugs, especially if combined with corticosteroids, commonly cause gastric ulcers or erosions by inhibiting prostaglandin synthesis and reducing mucosal blood flow and mucus production [32,33]. Paraneoplastic syndromes (ie, gastrinoma, mast cell tumors) and locally infiltrative tumors (ie, lymphoma, carcinoma) are probably more common causes of duodenal ulceration in dogs [32]. Cats rarely develop gastric or duodenal ulcers, with less than 40 reported cases [34]. In our experience, lymphoma is a major cause.

Ulcers may occur in any age or breed of dog or cat. Clinical signs vary from anorexia or mild vomiting and hematemesis to severe acute signs referable to perforation, obstruction, or catastrophic blood loss [32]. Melena may only be noted with severe blood loss and must be distinguished from dark-colored normal stool. Although ultrasound may identify ulcers, they are best visualized endoscopically. Many ulcers are not apparent when the serosal surface is visualized at surgery. Duodenal ulcerations or erosions, such as those seen with gastrinomas, may be difficult to recognize. Although some duodenal ulcers may appear as obvious craters, duodenal erosions can also appear grossly as bits of exudate adherent to the mucosal surface (Fig. 8).

Treatment includes identification and removal of the underlying cause when possible and supportive fluid or transfusion therapy as needed. Perforated or severely hemorrhaging ulcers should be surgically resected [32]. Mild cases can be managed with histamine-2 receptor antagonist drugs initially, with proton pump inhibitor use reserved for severe or refractory cases. Sucralfate, a cytoprotective drug, may also aid in reducing gastric mucosal injury by adhering to the ulcer bed, stimulating prostaglandin and mucus production, and inactivating pepsin [32].

Chronic intussusception

Intussusception occurs when one segment of the GI tract invaginates into the lumen of an adjacent segment. Although most commonly found at the ileocolic junction, intussusception may occur anywhere within the GI tract. Acute gastroenteritis (eg, parvoviral enteritis, parasites) is probably the most common cause of intussusception [35]. Most affected dogs are less than 1 year of age and have diarrhea with or without vomiting [36,37]. Cats,

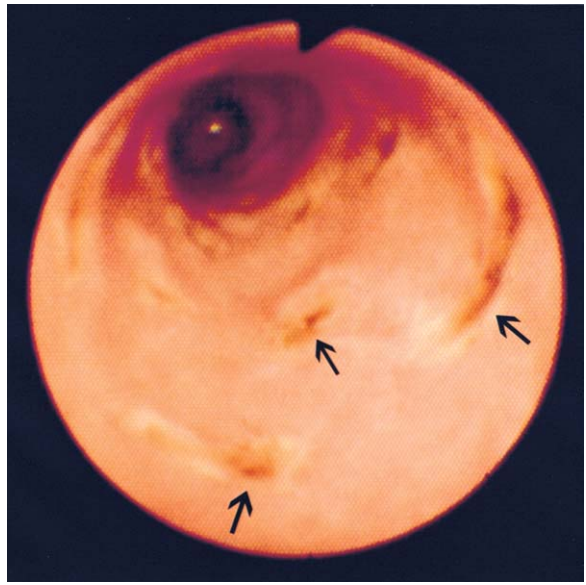

Fig. 8. Endoscopic view of the duodenum of a dog with a gastrinoma. There is multifocal duodenal ulceration represented by the areas of apparent exudate (*arrows*).

although uncommonly affected, may present at greater than 1 year of age, and postparturient queens seem to be at increased risk [38].

Although biochemical results were reportedly normal in one large case series, detailed laboratory findings have not been described in the veterinary literature [37]. An informal study of the records of 89 dogs and cats with intussusceptions presented to Texas A&M University in the past 25 years was performed, and 68 had a serum biochemical profile performed (Table 5). Sixty-six percent of dogs and the same percentage of cats were hypoproteinemic. Although less than half of these animals had a urinalysis performed and none had liver function testing, few had evidence of proteinuria or biochemical changes suggestive of HI. Because intussusception commonly occurs secondary to an underlying GI disease, concurrent disease states accompanying intussusception may play a significant role in the pathogenesis of hypoproteinemia.

Intussusceptions can sometimes be palpated in the cranial or ventral abdomen, but abdominal ultrasound is the most sensitive and specific noninvasive diagnostic test. Any relatively young dog with an apparent PLE should be checked for parasites and chronic intussusception. In particular, puppies with "chronic parvovirus" should be examined for an intussusception. Surgical treatment is usually required, but recurrence occurs in up to 20% of cases [36]. The prognosis is generally favorable in uncomplicated cases with preservation of the ileocolic valve.

Table 5
Biochemical abnormalities in 68 dogs and cats with gastrointestinal intussusception (1978–2002)

Biochemical abnormality	No. dogs affected (%)	No. cats affected (%)
Hypoproteinemia	41/62	4/6
Hypoalbuminemia	22/62	2/6
Hyponatremia	25/62	1/6
Hypokalemia	15/62	1/6
Hypochloridemia	18/62	2/6
Elevated ALP	13/62	0/6
Proteinuria or UPC > 1.0	2/12	0/4

Abbreviations: ALP, serum alkaline phosphatase; UPC, urine protein:creatinine ratio.

Gastrointestinal parasites

Heavy burdens of hookworms, whipworms, or other parasites may be associated with PLE. Prepatent infections may occur in any age of animal with massive acute exposure and may be difficult to diagnose [39]. Multiple fecal flotations (a minimum of three) should be performed in animals with chronic diarrhea, and empiric deworming with fenbendazole is also recommended. Positive fecal results confirm parasitism but not that the parasites are causing PLE. Several reported dogs with PLE did not respond when treated for endoparasitism; parasites may occur concurrent with other GI diseases or incite inflammation that persists after resolution of endoparasitism [14,19].

Intestinal crypt lesions

Intestinal lesions characterized by large numbers of dilated intestinal crypts filled with mucus, sloughed epithelial cells, and occasional inflammatory cellular debris have been reported in association with PLE in the dog [13,40]. It is unknown if the crypt dilation is a primary cause of GI protein loss or if these crypt lesions are simply a marker for another underlying intestinal disease. Tissue samples must include the full thickness of intestinal mucosa; superficial biopsies routinely miss the lesions [13]. Lesions may not be apparent in every histopathologic section, so it is important to obtain multiple samples. Numbers of affected crypts should be quantified, because even though large numbers of diseased crypts have been reported in animals with PLE, infrequent crypt lesions may be seen in clinically normal dogs [13]. Appropriate therapy for intestinal crypt lesions is currently uncertain. Two of four dogs treated in one case series responded to immunosuppressive, dietary, and antibiotic therapy [13].

Gut edema

GI protein loss increases during hypoproteinemia and volume expansion with crystalloid fluids, a phenomenon presumed to be caused by an increase

in mucosal interstitial fluid pressure [24]. It seems possible that if PLE or another disease process were to cause severe hypoalbuminemia with subsequent gut wall edema, the edema might become a cause for additional GI protein loss. Whether this spontaneously occurs in dogs is unknown; however, we have seen rare patients in which a diagnostic workup failed to reveal anything besides gut edema. Although it is possible that there was a focal lesion missed by biopsies, therapy for lymphangiectasia had a minimal clinical effect. Subsequent aggressive colloidal osmotic support (hetastarch or plasma) to minimize gut edema seemed to be beneficial.

Summary

GI protein loss can result from a heterogeneous group of diseases, including lymphangiectasia, IBD, neoplasia, ulceration, intussusception, and histoplasmosis. PLE should be suspected in any hypoalbuminemic patient with no evidence of exudative protein loss, proteinuria, or HI. A minimum laboratory database for the suspected PLE patient should include a complete blood cell count, a biochemical and electrolyte profile, urinalysis ($\pm$ urine protein:creatinine ratio), and pre- and postprandial bile acid determinations. Fecal α_1-PI concentrations may be used to confirm the presence of GI protein loss in cases with concurrent renal or hepatic disease. Because PLE is a syndrome and not a specific disease, the most effective therapy must be directed at the underlying cause. Multiple high-quality endoscopic biopsies are sufficient to diagnose most patients with PLE, although full-thickness biopsies are required in some cases. Patients with PLE are often clinically ''fragile,'' and careful symptomatic therapy must be integrated with dietary and medical management strategies in most cases.

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