Focus on protein-losing enteropathies in dogs

***Isuru Gajanayake*, from Willows Veterinary Centre and Referral Service**, **discusses the causes, diagnosis and the nutritional and medical management of canine PLE.**

A protein-losing enteropathy (PLE) can be defined as decreased serum proteins due to gastrointestinal disease. Both serum albumin and globulin are usually affected (termed panhypoproteinaemia) but the hypoalbuminaemia is usually more severe and more clinically relevant. Hypoalbuminaemia can generally be classified as mild (i.e., between 20 and 25 g/l), moderate (i.e., between 15 and 20 g/l) or severe (i.e., less than 15 g/l). In most cases of PLE, the hypoproteinaemia is moderate to severe. Similar (moderate to severe) magnitudes of hypoalbuminaemia can also be caused by hepatic functional impairment (e.g., portosystemic shunts, liver failure) and renal disease (i.e., protein-losing nephropathies). There are several other causes of mild hypoalbuminaemia including malnutrition, a negative acute phase response, exudative skin disease, external blood loss and as a compensatory response (to hyperglobulinaemia).

The most common causes of PLE in dogs include chronic inflammatory enteropathies, lymphangiectasia and neoplasia. The inflammatory enteropathies include food responsive enteropathies, dysbiosis and idiopathic inflammatory bowel disease. Lymphangiectasia most commonly occurs secondary to inflammation but can also occur as a primary lymphatic disorder in young dogs of certain breeds (e.g., Soft Coated Wheaten Terrier). Any diffuse cancer of the gut can cause a PLE but in dogs this is usually associated with high-grade lymphoma or small cell lymphoma.

The most commonly reported breeds with PLE include Yorkshire Terriers, Border Collies, German Shepherd Dogs and Rottweilers.[1] The typical clinical signs are usually gastrointestinal in origin (i.e., reduced appetite, weight loss, vomiting and diarrhoea). Physical examination findings include those related to malnutrition (i.e., poor body and muscle condition scores). Signs related to ascites (abdominal distension) and pleural effusion (dyspnoea, decreased lung sounds) may also be noted (Figure 1).

Diagnostic investigations

Laboratory testing

The combination of gastrointestinal signs (e.g., vomiting, diarrhoea, inappetence, weight loss) together with moderate to severe hypoalbuminaemia and concurrent hypoglobulinaemia is usually sufficient to confirm the presence of a PLE. In some cases, further tests will need to be performed to rule out the other two main causes of significant hypoalbuminaemia including kidney disease (with urine protein creatinine ratio quantification) and liver disease (with bile acid stimulation testing in a non-icteric dog). If finances are limited, these tests can be omitted provided there is no proteinuria on urine dipstick analysis and no biochemical changes suggestive of a hepatopathy on blood tests.

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FIGURE 1: Ascites and malnutrition in a 2-year-old Labrador Retriever secondary to a protein-losing enteropathy.

It should be noted that some dogs with PLE can have concurrent proteinuria or increased dynamic bile acids, so these results must be interpreted with caution.

Additional testing in dogs with suspected PLE include faecal analyses and serum cobalamin measurement. Faecal analysis for endoparasites and Giardiasis is particularly important in young dogs with PLE. Decreased serum B12 has both diagnostic and therapeutic implications in PLE. Serum cobalamin values less than 400 ng/l can indicate significant malabsorptive disease in PLE and warrants supplementation (see later section). There are currently no reliable and commercially available direct laboratory tests for protein malabsorption in dogs. Although food allergy testing using blood (or even hair) is commercially available, these tests are not recommended due to their poor specificity.

Diagnostic imaging

Abdominal imaging is often an important part of the investigation of PLE for several reasons including:

- To confirm the presence of gut disease
- To exclude other causes of hypoalbuminaemia such as liver and kidney disease
- To ascertain the underlying cause of the PLE (e.g., evidence of neoplastic versus inflammatory changes to the intestine)
- To check for secondary effects of PLE (such as ascites and thromboses).

The imaging can be performed using ultrasonography or computed tomography. When a PLE is strongly suspected based on the clinical and biochemical findings, the main reason for imaging is to check for the presence of intestinal neoplasia (particularly in middle-aged to older dogs). This may be highlighted by gut wall mass lesions, thickening of the intestinal wall with loss of layering detail and/or lymphadenopathy. Where signs of neoplasia are present on abdominal imaging, sampling for cytology can be performed. Ultrasonography may also highlight non-neoplastic gut wall changes such as those related to inflammation (e.g., muscularis layer thickening) and lymphangiectasia. The latter may be suspected on abdominal ultrasonography by the presence of perpendicular hyperechoic lines in the gut wall (Figure 2).

Gastrointestinal biopsies

Gastrointestinal biopsy samples can be collected by surgery or via endoscopy. Surgical biopsies provide a small number of better quality (full thickness) specimens, whereas endoscopic biopsies provide more numerous samples and are associated with less morbidity. In the presence of moderate to severe hypoalbuminaemia and especially with ascites, the risks of surgical gut biopsies generally outweigh the benefits due to the risk of dehiscence and septic complications. A surgical approach also incurs a delay before corticosteroid treatment can be instigated. For these reasons, endoscopic gut biopsies are preferred for most cases of PLE.

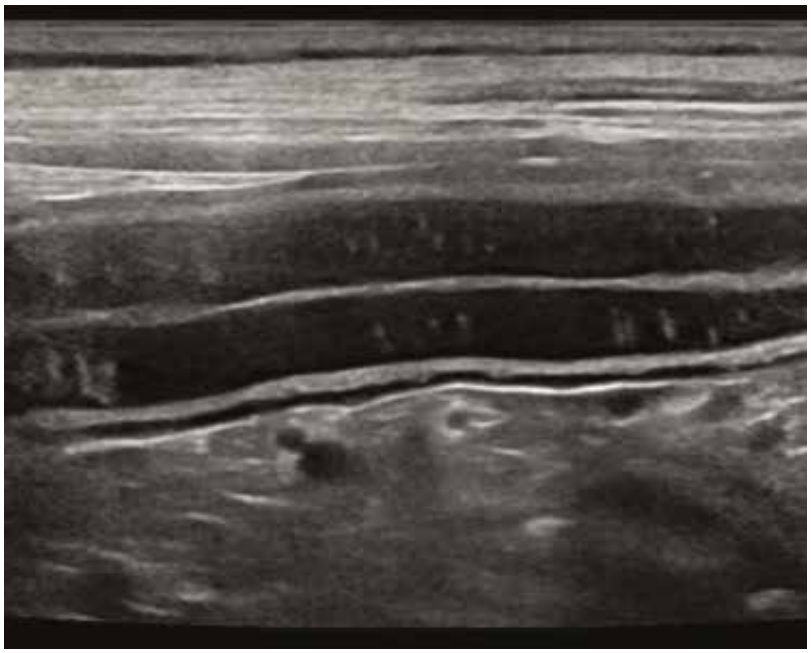

FIGURE 2: Abdominal ultrasound image from a 9-year-old Pug with a suspected PLE showing hyperechoic perpendicular mucosal striations suggestive of lymphangiectasia.

Short-term oncotic support can be provided with blood products to facilitate safer general anaesthesia for endoscopy and biopsy.

In many cases of PLE however, biopsies are not essential because a provisional diagnosis of inflammatory PLE can be made based on the signalment (young to middle-aged dog), clinical history (chronic signs) and imaging (no mass lesions or severe lymphadenopathy noted).

Lymphangiectasia in the form of lacteal dilation is commonly noted in many intestinal biopsies with inflammatory change. Where there is lacteal dilation without inflammation or if there is discordance between the two findings (i.e., severe lacteal dilation with minimal inflammation), the possibility of primary lymphangiectasia needs to be considered.

Nutritional management of PLE

Dietary fat restriction

Dietary fat restriction is one of the key nutritional interventions used to address PLE in people and dogs. Fat restriction reduces protein loss from the gut lumen due to reduced lymphatic flow. The magnitude of fat restriction needed to achieve a therapeutic effect is, however, unknown. Generally, a fat content of less than 20% calories from fat is considered low fat. The main commercial fat restricted diets available have approximately 17–19% of fat calories. A much lower fat content of 10–12% fat calories, so called ultra-low-fat diet, can be achieved with a balanced home-cooked diet. Assessment and comparison of diets for their fat contents requires conversion of the 'as fed' dietary fat content to the fat content on energy/calorie basis. This conversion can be simplified by use of an online guaranteed analysis converter (**https://balance.it/convert**).

Hydrolysed and novel protein diets

To address suspected or confirmed inflammatory intestinal disease causing PLE, a hydrolysed protein diet or a novel protein diet is often necessary. This is especially important for the long-term management of the underlying gut disease e.g., after the serum proteins have normalized. There are a number of commercial hydrolysed protein diets available for this purpose. In addition to this, several single protein diets are also available, including those based on unusual proteins such as venison, rabbit and insect protein, which may be novel protein options depending on the diet history of a particular patient.

Combined low fat and hydrolysed protein diets

When choosing a commercial diet for a dog with PLE, there can be some conflict between choosing a fat restricted diet or a hydrolysed/novel protein diet. If a choice has to be made in these situations, dietary fat restriction should take priority over a hydrolysed/novel protein diet in the initial stages. Once the serum proteins have improved, the dog can be transitioned to a hydrolysed or novel protein diet with a higher fat content but with careful monitoring for recurrence of hypoproteinaemia.

Ideally, dogs with inflammatory PLE should be fed diets which are concurrently both fat restricted and based on single hydrolysed or novel proteins. Currently there are three commercial diets that meet these criteria including Royal Canin® Gastrointestinal Low Fat + Hypoallergenic dry food, Dechra Specific Digestive Support Low Fat wet and dry food, and Hill's z/d Low Fat dry food.

Balanced home-cooked diets

Feeding a balanced home-cooked diet can be a useful way to manage dogs with inflammatory PLE. This is because home-cooked diets can be formulated with the dual nutritional requirements of fat restriction and novel protein provision. A balanced home-cooked diet can also be formulated to be ultra-low-fat (i.e., 10–12% of fat calories) which can be more effective than commercial fat restricted diets in some dogs. Despite these potential benefits, balanced home-cooked diets require formulation by a veterinary nutritionist and the addition of a micronutrient supplement(s) to ensure the food is complete and balanced.

Nutritional supplements

If the serum B12 is less than 400 ng/l, regardless of the underlying pathology, cobalamin supplementation is recommended. Supplementation can be provided by injectable hydroxocobalamin by weekly subcutaneous injections for 6 weeks, followed by a single injection 4 weeks later. Alternatively, oral supplementation can be given daily for 12 weeks. In both cases, serum B12 should be rechecked 4 weeks after the last dose.

Medium chain triglycerides are used in people to manage PLE as these are thought to be absorbed directly into the portal vasculature rather than via the dysfunctional lymphatic system. A similar effect may not be evident in dogs and medium chain triglycerides can also be unpalatable to many dogs.

Feeding tubes

For dogs severely affected by their PLE, enteral nutrition support may be necessary. This can be in the form of a nasal feeding tube (i.e., naso-oesophageal or naso-gastric), or an oesophagostomy feeding tube. Gastrostomy tubes (both surgically and endoscopically placed) would carry a higher than usual risk of complications due to the hypoalbuminaemia.

A recent retrospective study into the use of feeding tubes in dogs with PLE reported a potential survival advantage when enteral feeding was instituted.[2] In that study, dogs with inflammatory PLE which were treated with enteral feeding and immune-suppressive treatment were nearly seven times more likely to survive compared to those without a feeding tube.

Medical management of PLE

Supportive medications

Dogs with PLE usually benefit from supportive measures in the short term including fluid therapy (to correct fluid deficits, acid-base disturbances and electrolytes deficiencies) and other such measures (e.g., anti-emetic therapy, anti-diarrhoeals, etc.). Fluid oncotic support in the form of blood products are likely only to be helpful in the short term. Abdominocentesis as a therapeutic measure is also unlikely to be beneficial as the ascites usually re-develops within days. Some caution should also be exercised when draining a large volume of abdominal fluid as this can affect the circulating blood volume and lead to signs of hypoperfusion. Conversely, thoracocentesis is advisable, even as a repeated measure, due to the discomfort associated with a pleural effusion.

Antithrombotic medications

Dogs with PLE have a high risk of thrombotic complications, including aortic thromboembolism.[3] Testing for thrombotic risk is not straightforward because patient-side tests such as thromboelastography are needed. To reduce the possible thrombotic risks, clopidogrel or aspirin is recommended; however, these medications can cause or increase the risk of gastrointestinal haemorrhage so should be used with caution where bleeding is suspected due to the underlying gut disease.

Immune-suppressive therapy for inflammatory PLE

Corticosteroids

Corticosteroids in the form of injectable dexamethasone and oral prednisolone remain the mainstay treatment for inflammatory PLE. These medications are cheap, effective and have a rapid onset of action. Corticosteroid adverse effects can however be seen, which is the main limitation of this medication. This author prefers a maximum prednisolone dose of 1 mg/kg per day for immune-mediated gut disease in dogs. In large and giant-breed dogs, a lower dose may be appropriate.

Chlorambucil

Several alternative immune-suppressive agents have been used to manage PLE in dogs, either to enhance the effect of steroids or as steroid-sparing agents where corticosteroid adverse effects are noted. Chlorambucil has become the preferred second agent for PLE in dogs in recent years, based on a publication showing its superiority to azathioprine.[4]

Chlorambucil dosing is based on body surface area i.e., 2–6 mg/m^2 once daily. This medication is only available as 2 mg tablets (under the cascade system), which should not be split due to their cytotoxicity. For this reason, the calculated oral dose must be administered in multiples of full tablets daily, or a tablet given every 2 to 4 days in smaller dogs. Chlorambucil can cause gastrointestinal signs and myelosuppression as adverse effects, with the latter requiring intermittent blood tests (complete blood count) for monitoring. Chlorambucil is also expensive and requires careful handing (with appropriate health and safety precautions) as it is a cytotoxic agent.

Ciclosporin

Ciclosporin is available in both liquid and capsule formulation for use as a second line immune-suppressive agent. This medication is expensive but is generally well-tolerated with intermittent gastrointestinal signs being the most commonly reported adverse effect. A starting dose of 5 mg/kg once a day is often used but some dogs require double that dose (5 mg/kg q12h) which comes at a higher cost and greater risk of adverse effects.

Novel therapies

Octreotide, a somatostatin analogue, is used to treat primary intestinal lymphangiectasia in people. It is thought to decrease lymphatic fat absorption and thus aid in PLE similar to a fat restricted diet. The use of this medication has also been reported in a small number of dogs, with questionable efficacy but a low rate of adverse effects.[5] In that study, the medication was administered once daily by subcutaneous injection. Octreotide is expensive and can be difficult to source.

Clinical approach to canine PLE

The clinical approach to dogs with PLE can be tailored depending on their clinical severity and the confidence in the diagnosis. When the clinical signs are relatively mild (regardless of the severity of the hypoproteinaemia), a nutritional intervention is the logical first step. This is also the preferred approach to cases where limited diagnostics have been performed (e.g., blood tests only).

The preferred initial nutritional approach to an inflammatory PLE (presumed or confirmed) is a

combination of a fat restricted diet and a single hydrolysed or novel protein. These specifications can be provided by both commercial diets and a balanced home-cooked diet. If this combined approach is not possible, dietary fat restriction should be favoured initially over the protein source (i.e., hydrolysed or novel).

The main clinical parameters that require monitoring in PLE include bodyweight, appetite, stool quality and vomiting. Blood tests should ideally be performed to measure serum albumin and globulin approximately 1–2 weeks after commencement of therapy. If these blood tests are not financially feasible, in-house measurement of total solids (from a microhematocrit tube using a refractometer) can be a reasonable economical alternative.

For dogs that have severe clinical signs or are refractory to nutritional modulation, immune-suppressive therapy is often indicated from the outset; however, it should be noted that some dogs with severe signs can respond to dietary manipulation alone. If gastrointestinal biopsies have not been performed prior to starting immune-suppressive therapy, this should be discussed with appropriate importance depending on the clinical suspicion for neoplasia (i.e., based on the clinical history and imaging). In cases of empirical treatment, the risks should be clearly outlined. The preferred initial approach to immune suppression in inflammatory PLE is with corticosteroids. If this group of medications are ineffective, a second line agent such as chlorambucil or ciclosporin should be considered.

In dogs with severe refractory disease, alternative therapies may need to be considered. This can include feeding an ultra-low fat balanced home-cooked diet (based on a single novel protein) instead of a commercial diet. Alternative medications can also be attempted at this stage, including use of ciclosporin instead of chlorambucil (or vice versa) and octreotide.

About the author

Isuru Gajanayake graduated with a Bachelor of Veterinary Science from the University of Sydney in 1998. After several years working in general practice in Australia and England, he completed a combined residency in Small Animal Internal Medicine and Small Animal Nutrition at the Royal Veterinary College (London). Isuru now works at Willows Veterinary Centre and Referral Service as an American, European and RCVS Recognized Specialist in Small Animal Medicine and as an American Board-Certified Veterinary Nutritionist.

Reflect on your reading

1. The ideal nutritional management of a PLE includes both:
   a. Protein restriction and a hydrolysed/novel protein
   b. Fat restriction and protein restriction
   c. Fat restriction and a hydrolysed/novel protein
   d. Protein restriction and a vegetable protein diet

2. An ultra-low-fat diet is:
   a. A commercial diet containing 17–19% fat calories
   b. A home-cooked diet containing 10–12% fat calories
   c. Used to manage concurrent pancreatitis with PLE
   d. Made from medium chain triglycerides

3. The preferred initial immune-suppressive agent in inflammatory PLE is:
   a. Prednisolone
   b. Ciclosporin
   c. Chlorambucil
   d. Octreotide

4. Gastrointestinal biopsies in PLE:
   a. Are needed to differentiate a PLE from a PLN
   b. Should be full thickness biopsies collected by surgery
   c. Can be safely collected by endoscopy
   d. Are only required for primary lymphangiectasia

5. The possible sequalae of PLE includes:
   a. Ascites
   b. Pleural effusion
   c. Aortic thromboembolism
   d. All of the above

Answers available online in the BSAVA Library.

References and further reading are available at: **www.bsavalibrary.com**.

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