Canine Intestinal Lymphangiectasia

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ABSTRACT: Intestinal lymphangiectasia (IL) is the dilation of lymph vessels in the intestine and is one of several causes of protein-losing enteropathy in dogs. IL is an uncommon disease in the general canine population but is one of the more common causes of gastrointestinal protein loss. Canine IL most commonly presents as a complication of inflammatory diseases in the intestine or mesentery but can occur secondary to other causes of lymphatic or venous obstruction. IL is a disease primarily of middle-aged dogs but can affect dogs at almost any age. Although any breed can be affected, those considered predisposed to IL include basenjis, Lundehunds, soft-coated wheaten terriers, and Yorkshire terriers. The definitive diagnosis of IL is based on histologic demonstration of characteristic intestinal lacteal dilation. Therapy consists of treating the underlying disease, when identified, and a low-fat diet. The long-term prognosis of affected dogs is usually guarded because many have a poor response to therapy.

First described in dogs in 1968, intestinal lymphangiectasia (IL) is characterized by dilation of intestinal lymph vessels in the mucosa, submucosa, or both; dilation of mesenteric lymph vessels is also common. IL is one of several causes of protein-losing enteropathy (PLE) in dogs. This article gives an overview of canine IL, including the etiology and pathogenesis, associated clinical signs, diagnostic findings, and treatment strategies.

PATHOGENESIS AND CAUSES

IL can be congenital (primary) or acquired (secondary). Most human cases are considered congenital, reflecting generalized malformation of lymph vessels, such as aplasia. Clinical disease is observed primarily in children and young adults and can be associated with limb edema and chylous effusions in the thorax, abdomen, and scrotum. In contrast to human IL, canine congenital IL is considered less common than acquired IL. To date, affected dogs have not had lymph vessel abnormalities in the absence of inflammation as has been described in humans. A small number of dogs reported in the literature may have had primary lymphangiectasia, but lymphangiography was not performed to demonstrate widespread lymph vessel abnormalities.

Acquired IL can be caused by increased pressure in lymph vessels. Canine IL is recognized most frequently in the setting of intestinal or mesenteric disease in which inflammatory processes are suspected to block lymph flow. Primary neo-
plasms in the intestinal wall or mesentery or metastatic tumors in the mesenteric lymph nodes could also obstruct lymph flow but are not seen as often in dogs with IL.

Acquired IL can also result from diseases that increase venous hydrostatic pressure. Right-sided heart failure, pericardial effusion, pericarditis, or other diseases that increase venous pressure at sites where the thoracic duct enters the systemic circulation can lead to lymphatic congestion and lymphangiectasia. The prevalence of IL in dogs with these diseases is not described because these patients would be unlikely to undergo gastrointestinal (GI) biopsy.

When pressure in the mesenteric or intestinal lymph vessels increases, the intestinal villous lacteals can dilate, become more fragile, and rupture easily. Lymph leaks from the ruptured lacteals into the intestinal lumen, carrying all its contents, such as chylomicrons, lymphocytes, and proteins, including albumin and immunoglobulins.\(^4,6–8\) Some lymph constituents, especially proteins, can be digested and reabsorbed at more distal sites in the intestine. However, the presence of lymphangiectasia, inflammation, or edema in the mucosa can limit intestinal absorptive capacity, resulting in a net loss of lymph. Blood concentrations of lymph constituents (i.e., protein, lipids, lymphocytes) then reflect the balance between synthesis and intestinal loss.

When canine IL develops secondary to inflammatory disease of the small intestine or lymph vessels, the events initiating or perpetuating inflammation are usually unknown. One hypothesis suggests that affected animals may be hypersensitive to a luminal protein, perhaps dietary or bacterial, leading to inflammation and increased permeability of intestinal blood vessels.\(^9\) The resultant edema is thought to act as a pressure barrier to lymph flow from the intestine, causing dilation of lacteals.\(^9\) Another hypothesis accounts for the presence of lipogranulomas observed in the lymph vessels of many dogs with IL. Lipogranulomas are thought to be elicited by a proinflammatory lipid substance present in the intestinal lymph of some dogs. In this scenario, the inflammatory lipid produces a regional lymphangitis and lymphadenitis with formation of lipogranulomas that obstruct lymph flow.\(^7,8\) The lipid implicated in lipogranuloma formation is unknown. Lipogranulomas are not considered important in the pathogenesis of IL in other species.

Although dogs of any breed can develop IL, apparent breed predilections imply the possibility of a genetic component to disease development. Although there is no recognized breed predilection for congenital IL, acquired disease appears to be more common in Yorkshire terriers.\(^10\) Breeds with a higher incidence of IL due to inflammatory diseases include basenjis, soft-coated wheaten terriers, and Lundehunds. These breeds appear to be predisposed to lymphoplasmacytic enteritis with shortening and fusion of the mucosal villi and eventual blockage of small intestinal lymphatics.\(^11–13\)

**CLINICAL FINDINGS**

The clinical signs of IL can be quite variable. Many dogs with IL exhibit nonspecific signs, such as anorexia or lethargy; however, dogs may exhibit polyphagia.\(^14\) As indicated in Figure 1, diarrhea is one of the most consistent clinical signs referable to the GI tract but is not seen in all patients with IL.\(^15\) When diarrhea is not a presenting complaint, IL should not necessarily be ruled out if otherwise compatible signs, such as weight loss, edema, or ascites, are present. Vomiting is also a frequent clinical sign in dogs with IL. Dilation of intestinal lymphatics alone does not seem to cause vomiting, but because many dogs with IL have intestinal inflammation, vomiting likely results from inflammatory stimuli.

Ascites, subcutaneous-dependent edema, and hydrothorax are common in IL patients. In most cases, fluid accumulates secondary to decreased colloid oncotic pressure from hypoproteinemia, especially hypoalbuminemia. Effusions or edema may develop when serum albumin concentrations fall below 1.5 g/dl; effusions in these situations are usually pure transudates. However, pure transudates can sometimes be seen in the context of serum albumin concentrations higher than 1.5 g/dl, suggesting that other factors, such as increased hydrostatic pressure or lymphatic obstruction, may contribute to fluid accumulation. Modified transudate ascites has also been described in a dog with IL.\(^6\) Chylothorax has been reported in three dogs\(^5,16\) and
has been observed in some patients with IL at the Washington State University Veterinary Teaching Hospital. In animals with chylous effusions, generalized abnormalities of lymphatics and lymph flow involving the GI tract and body cavities are likely.

In some dogs, clinical signs of thromboembolic disease, such as tachypnea and hyperpnea due to pulmonary thromboemboli, can develop. Thromboembolism can develop if there is an imbalance between pro- and anticoagulant factors, but the coagulation abnormalities in dogs with IL, or other causes of PLE, are poorly characterized and understood. An imbalance favoring a prothrombotic state could develop from GI loss of antithrombin III, an anticoagulant protein of a comparable size to albumin. In cases of PLE induced by IL, evidence of hypoglobulinemia suggests that loss of larger proteins, such as coagulation factors, may also occur. An imbalance between pro- and anticoagulant factors is also possible if underlying inflammatory disease has enhanced the production of procoagulant factors. Thus loss of both antithrombin III and coagulation factors could still result in a balance tipped toward hypercoagulability and lead to thromboembolism. Glucocorticoids, commonly used in treating canine IL, can enhance the production of procoagulant factors and may also play a role in tipping the balance toward a prothrombotic state in these patients. Increased platelet aggregability or vascular endothelial injury, both of which have been documented in humans with inflammatory bowel diseases, may also contribute to hypercoagulability.

LABORATORY TESTING

Laboratory abnormalities in dogs with IL may reflect intestinal loss of lymph but are neither pathognomonic nor specific for the disease. Lymphopenia is the complete blood count abnormality most supportive of IL. The absence of lymphopenia in a dog exhibiting clinical signs consistent with PLE would make IL somewhat less likely. Anemia of chronic inflammation and neutrophilic leukocytosis (due to a stress leukogram or chronic inflammation) may be observed in some dogs. Platelet counts may be normal or increased as a consequence of chronic inflammation. Thrombocytopenia in a dog with IL is unusual and suggests a complication of the disease, such as thromboembolism or disseminated intravascular coagulation.

Hypoalbuminemia is the most consistent laboratory abnormality reported in canine IL, and in one study, the magnitude of hypoalbuminemia generally reflected the histologic severity of the disease. Some dogs, however, have normal albumin levels, which may reflect more focal IL. Commonly, serum globulin concentration is also low. In some breeds, especially basenjis and Lundehunds, in which IL is considered secondary to severe intestinal inflammation, globulins can be normal or increased secondary to increased production associated with the inflammatory process.

Total serum calcium level is often decreased as an artifact of low serum albumin concentration. Occasionally, the total corrected calcium concentration remains abnormally low. In two studies, ionized calcium concentrations were abnormally low in all patients in which it was measured. Hypocalcemia may develop from decreased intestinal calcium absorption secondary to impaired absorption of fat and fat-soluble vitamin D. Formation of calcium-lipid precipitates has also been implicated in the pathogenesis of hypocalcemia in dogs with IL. Occasionally, hypocalcemia is severe enough to cause clinical signs, such as seizures. If the serum magnesium level is measured, dogs with IL may also have hypomagnesemia.

Other biochemical abnormalities seen in dogs with IL include hypocholesterolemia and increased alanine aminotransferase and alkaline phosphatase activity. Hypocholesterolemia is attributed to GI loss and lipid malabsorption. Increases in liver enzyme activities could be a reflection of some degree of concurrent hepatobiliary disease. Vacular changes in hepatocytes have been described in dogs with IL and increased liver enzyme activities, whereas some dogs with increased liver enzyme activities had no apparent histologic lesions in the liver.

Urinalysis results are typically unremarkable in dogs with IL, and there are no urinalysis abnormalities that would point to the possibility of IL. However, urinalysis results are important to rule out hypoalbuminemia from renal losses, especially in dogs that are hypoalbuminemic with normal serum globulin concentrations. A urine protein:creatinine ratio less than 1 generally excludes the kidneys as a major site of protein loss, but higher ratios do not eliminate GI albumin loss. It has been speculated that in some dogs with IL, increased permeability of the GI tract to luminal antigens and immune responses against those antigens may eventually lead to immune complex formation and proteinuria secondary to glomerulonephritis.

DIAGNOSIS

The diagnosis of IL in dogs can be challenging. Thorough physical examinations and laboratory assessments are important in patients with chronic vomiting, diarrhea, or weight loss to exclude non-GI causes of

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\text{Corrected calcium} = \frac{(3.5 - \text{Measured albumin}) + \text{Measured calcium}}{\text{Measured albumin}}
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these signs. Panhypoproteinemia can suggest the possibility of a PLE, such as IL. In dogs with hypoalbuminemia only, it may be important to evaluate other causes, such as decreased hepatic production or urinary or third-space losses. Normal fasting and fed bile acids would make decreased production an unlikely cause of hypoalbuminemia, and fluid analysis of effusions should, in the majority of cases, eliminate albumin loss into body cavities as a factor contributing to hypoalbuminemia.

A number of methods can demonstrate GI protein loss in cases of suspected PLE. However, these assays, which include measurement of excreted radioactive labeled albumin\(^4\),\(^{12}\),\(^{25}\) or detection of such compounds as polyvinylpyrrolidone, dextran, or ceruloplasmin in the feces are often restricted to clinics capable of handling radioactive substances or with cages that can strictly separate feces from urine. Recent work suggests that measurement of fecal \(\alpha_1\)-protease inhibitor is a simple, noninvasive, and objective method of documenting abnormal GI protein loss in dogs.\(^31\) In normal dogs, \(\alpha_1\)-protease inhibitor is not excreted to any appreciable extent into the intestinal lumen and, when present, cannot be digested by luminal bacteria. Increased fecal excretion of \(\alpha_1\)-protease inhibitor would be indicative of abnormal intestinal permeability consistent with PLE.\(^31\) Although useful for documenting GI protein loss, these tests still do not differentiate between the possible causes of PLE.

Thoracic radiography would be appropriate for patients with signs of respiratory disease that could reflect the presence of pleural effusion or thromboembolism or for assessing lymph node enlargement or other lesions consistent with neoplasia or systemic inflammatory disease. Plain abdominal radiography is usually not helpful in suggesting the presence of the disease.

Abdominal ultrasonography can be useful in evaluating dogs with GI disease. Abnormalities on abdominal ultrasonography described in dogs with IL include thickening of the small intestinal wall, hyperechoic mesentery, hyperechoic mucosal layer, indistinct wall layering, and small bowel hypermotility.\(^5\) Peritoneal effusion is also readily apparent during abdominal ultrasonography. Abdominal ultrasonography findings may not necessarily correlate with the severity of the disease\(^5\) and can be normal in dogs with IL, although most dogs with severe IL have ultrasonographic abnormalities. Technetium scans have been used in humans to evaluate congenital lymphatic abnormalities,\(^7\) but their use in dogs with IL has not been described.

Although potentially useful for demonstrating lymph vessel abnormalities, lymphangiograms have not been widely used in humans or dogs for diagnosing IL. In humans, lymphangiograms have helped define the congenital form of the disease as a reflection of widespread lymphatic abnormalities.\(^3\) The use of lymphangiography in a dog with IL has been reported only once, and information needed to characterize impaired lymph flow to specific regions of the body was limited.\(^16\)

Ultimately, definitive diagnosis of IL is made following histologic assessment of intestinal biopsies. Biopsies can be obtained endoscopically or via exploratory laparotomy. There are advantages and disadvantages to both techniques. Endoscopy typically is less costly and less invasive, an important issue in unstable animals. Endoscopy permits direct visualization of the mucosa, and dilation of lacteals in villous tips can be readily appreciated in some cases (Figure 2). To increase the size and visibility of the lacteals, giving a small high-fat meal 12 hours before the diagnostic procedure has been recommended.\(^20\) The primary disadvantage of endoscopic biopsies is that lymphangiectasia can be a focal disease occurring regionally in the intestine and thus could be missed because of short endoscope length, poor tissue sampling technique, or both. Some researchers have reported that lesions are scattered through the intestine,\(^7\) are more pronounced in the jejunum,\(^14\) or predominate in the duodenum with changes diminishing toward the ileum.\(^11\) Collectively, these observations emphasize that the lesions of canine IL cannot be reliably expected in any single location. Thus in the case of a negative biopsy result, lymphangiectasia should not necessarily be eliminated from the differential diagnosis if other aspects of the case are compatible. When endoscopy is used, samples from the duodenum and ileum should be acquired whenever possible to increase the likelihood of obtaining a diagnosis.
related to fluid support. Caution should be exercised when administering additional doses of plasma or human albumin in the days following the procedure because sensitized patients may be more susceptible to developing allergic transfusion reactions. Administration of colloid fluids (e.g., hydroxyethyl starch) can also be useful during the anesthetic period for maintaining plasma oncotic pressure and adequate effective circulating volume. Use of colloids has been associated with an increased risk of bleeding due to interaction with von Willebrand’s factor, but the risk of bleeding in dogs appears to be minimal if smaller doses (<6 ml/kg) are used.

If an exploratory laparotomy must be performed, it should also be considered that wound healing may be altered and the risk of suture dehiscence increased. Although the topic is controversial, hypoalbuminemia does not seem to impair wound healing after intestinal biopsies. However, intestinal pathology and malnourishment due to a generalized catabolic state may increase the potential for suture dehiscence. Poorly absorbable or nonabsorbable sutures used in conjunction with serosal patch grafting can help prevent dehiscence.

The histopathologic hallmarks of IL are markedly dilated lacteals or lymph vessels filled with proteinaceous fluid visible in one or more layers of the intestinal wall (Figure 4). In cases of primary lymphangiectasia, inflammatory cells are not noted in any layers of the intestine, except possibly lipogranulomas in the intestine. These conditions may be aggravated with crystalloid fluid therapy during the anesthetic period. Plasma transfusions or administration of human albumin (10 ml/kg of a 5% solution) before anesthesia may increase the albumin level short-term and reduce the chance of developing complications related to fluid support.
subserosa along the lymph drainage (Figure 5). In cases of secondary lymphangiectasia, inflammatory or neoplastic cells can be present in any segment of the intestine (the mucosa, muscularis, or subserosa), around lymph vessels, or in lymph nodes. The inflammation must be severe to produce a lymphatic blockage significant enough to cause lymphangiectasia; slight inflammation is not considered clinically important. The nature of inflammatory infiltrates varies among animals. In one retrospective study, inflammatory infiltrates ranged from lymphocytic–plasmacytic to lymphocytic to eosinophilic, with lymphocytic–plasmacytic inflammation being the most common.5

**TREATMENT**

Treatment of IL in dogs has three main thrusts: resolution of the underlying disease, when identified; dietary modification; and symptomatic therapy. It is not unusual to implement treatment regimens that address all three aspects simultaneously.

Because canine IL is most often secondary to an underlying disease, such as inflammatory bowel disease, neoplasia, or cardiac failure, treatment of the primary disease may improve the clinical course. Prednisone at immunosuppressive doses (2 to 4 mg/kg/day) is commonly used in the initial management of many dogs with IL observed in association with mucosal inflammation. In severe cases or patients that respond poorly to glucocorticoids alone, azathioprine (1 to 2 mg/kg or 50 mg/m² PO q24–48h) may be added. Dogs with minimal inflammation typically have poor responses to immunosuppressive/antiinflammatory therapy.

In humans with IL, dietary modification is considered the most important aspect of treatment. Dietary fat restriction, especially of long-chain triglycerides, is associated with increased concentration of serum proteins, including albumin; less severe histologic evidence of inflammation; and resolution of clinical signs.37,38 Diets very low in fat are believed to decrease lymph flow in the mesentery up to tenfold compared with high-fat diets and help decrease the pressure in the lymphatic system.39 Medium-chain triglycerides (MCTs) are added routinely to the diet of affected humans to increase the caloric intake without increasing lymph flow.

For many years, MCTs were recommended to increase the caloric intake of dogs on a very low-fat diet. The purported benefit was absorption of MCTs directly into the portal circulation instead of the lymphatics, thereby decreasing lymph production. However, studies in dogs have shown that MCTs, like long-chain triglycerides, are incorporated into chylomicrons and contribute to the composition of intestinally derived lymph.39,40 Whether the actual volume of lymph is reduced with MCT supplementation has not been established in dogs with IL. In a study of dogs with chylothorax, however, dietary MCT supplementation did not alter the volume of lymph flow through the thoracic duct.41 Long-chain fatty acids have proinflammatory properties,42 proposed as a cause of lipogranulomas. Thus feeding diets with a greater proportion of MCTs may diminish inflammatory stimuli while preserving the favorable aspects of dietary lipids. Therefore, it is possible that some dogs may still derive clinical benefits from the increased calories of MCT supplementation. The decision to use MCTs should probably be made on a case-by-case basis, and if used, responses should be judged by improvement in clinical signs; weight gain; and improvement in laboratory abnormalities, especially serum albumin.

Overall, dietary strategies for treating canine IL have met with mixed success. Some researchers have described increased serum protein concentrations and an improvement in edema associated with feeding a commercially available fat-restricted diet.14 One dog had good long-term results in association with feeding a fat-restricted diet supplemented with MCTs.25 Other
dogs have not exhibited changes in clinical status in response to prolonged (36 weeks) MCT supplementation in the diet, but it is unclear whether the dogs in these reports were also fed a low-fat diet. The authors have also seen varied responses to dietary changes in patients with IL.

Although not studied in detail, patients with IL may be prone to cobalamin deficiency as are dogs with other causes of maldigestion or malassimilation. It is believed that some dogs may experience diarrhea solely due to cobalamin deficiency. Therefore, measuring serum cobalamin concentration may be warranted in dogs with IL. Although prospective studies documenting efficacy in dogs with IL have not been conducted, if serum cobalamin concentration is below the reference range, supplementation may be considered at 50 μg/kg (up to 1000 μg) SC once a week for 6 weeks, then once every other week for 6 weeks, and then monthly. Supplementation may need to be continued long term because GI lesions may persist; administration frequency may be best determined by regularly measuring serum cobalamin concentration.

Symptomatic treatment of dogs with IL consists of transfusions of plasma or other colloids, typically to stabilize the patient before surgery. However, colloidal transfusion should be considered as only a short-term treatment because administered colloids are lost into the intestine. Diuretics may help relieve clinical signs from severe ascites and thoracic effusion. Thoracocentesis or abdominocentesis may be needed in some dogs to acutely alleviate the clinical signs or discomfort associated with the presence of effusions.

Despite the recognition that dogs with PLE can be predisposed to thromboembolic disease, guidelines for prophylaxis of thromboembolic disease have not been developed for dogs with IL or other causes of PLE. Thromboembolism prophylaxis is probably warranted in some cases, but neither criteria for selecting cases warranting prophylaxis nor reasonable protocols have been developed for such patients. Intuitively, dogs with severe hypoalbuminemia, thrombocytosis, or evidence of active inflammation may have a more urgent need for prophylaxis, but no controlled studies have supported such contentions. A possible anticoagulant with few side effects is low-dose aspirin (0.5 to 1 mg/kg bid). For dogs in acute stages of known or suspected thromboembolic disease, heparin, low-molecular-weight heparin, or warfarin is indicated. Therapy with warfarin, which is highly protein bound, is demanding because of inconsistencies of absorption from dog to dog and variations in plasma protein concentrations. Therefore, safe warfarin therapy requires close monitoring of coagulation parameters (prothrombin time, partial thromboplastin time). Low-molecular-weight heparin is attractive in terms of efficacy and safety but could be cost prohibitive for many cases. Thrombolytic drugs, such as urokinase, streptokinase, or tissue-plasminogen activator, can be considered in dogs with demonstrated thromboemboli and have been shown to be effective in managing acute thromboembolism in dogs with PLE, but the efficacy of these drugs has not been fully evaluated.

PROGNOSIS

The prognosis for dogs with IL partly depends on the underlying disease. If the underlying disease can be resolved, the prognosis is good. In cases in which the underlying disease cannot be effectively managed, the prognosis is guarded to grave. Many animals live for only a short time after the diagnosis is made and die as a result of disease complications. In all reported cases, the longest survival has been 2 years. Owners should be aware that although resolution of the disease may be achieved in a few cases, a more attainable goal may simply be control of clinical signs.

REFERENCES

5. Ascites in canine IL can be caused by which of the following?
   a. altered lymph flow in the mesentery
   b. loss of nutrients in the intestine due to diarrhea
   c. protein loss in the intestine and hypoproteinemia
   d. a and c
   e. b and c

6. The lack of diarrhea as a clinical sign
   a. rules out the diagnosis of IL.
   b. does not rule out the diagnosis of IL.
   c. indicates a very mild form of IL.
   d. indicates a primary congenital cause of IL.
   e. indicates a secondary inflammatory cause of IL.

7. Hypoalbuminemia in IL is seen when
   a. hepatic capacity for synthesis is outstripped by loss of albumin.
   b. albumin is lost into the intestinal lumen.
   c. protein content of the diet is too low.
   d. the fat:protein:carbohydrate ratio is not balanced.
   e. albumin leaks into an existent ascites.

8. A definitive diagnosis of canine IL is established on the basis of
   a. clinical signs.
   b. clinical signs and laboratory abnormalities.
   c. laboratory abnormalities and α1-protease inhibitor test.
   d. intestinal biopsies.
   e. lymphangiography.

9. Which of the following statements about MCTs is correct?
   a. In dogs, MCTs are absorbed from the intestine directly into the portal blood.
   b. MCTs are known for their proinflammatory properties.
   c. In dogs, MCTs are absorbed into the intestinal lymphatics like long-chain triglycerides.
   d. MCTs are necessary to improve caloric intake of dogs with IL.
   e. MCTs are not used as a dietary therapy of IL in humans.

10. Therapy for canine IL consists of which of the following?
   a. treatment of possible underlying diseases
   b. a low-fat diet and surgical excision of affected areas
   c. surgical excision of affected areas and symptomatic treatment
   d. treatment of underlying disease, a low-fat diet, and symptomatic treatment
   e. symptomatic treatment with diuretics and colloids