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Secondary intestinal lymphangiectasia in a dog - a case report

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ABSTRACT

This paper describes in detail the clinical and pathomorphological aspects of lymphangiectasia in a dog. The dog was presented at the Clinic for Internal Diseases, Faculty of Veterinary Medicine, Zagreb, after a period of chronic diarrhoea and progressive weight loss. Results of clinical examination indicated a protein-losing enteropathy due to lymphangiectasia. Adequate therapy was conducted, but with unsatisfactory results and the dog was euthanised at the owner's request. Secondary lymphangiectasia could be due to mononuclear lymphangitis (unknown etiology) which was confirmed pathoanatomically and pathohistologically, but secondary dilatation of lacteals could be the result of inflammatory bowel disease (lymphocytic and plasmocytic infiltration).

Key words: dog, protein losing enteropathy, lymphangiectasia, lymphangitis, pathological findings

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Introduction

Intestinal lymphangiectasia is a chronic protein-losing enteropathy found in humans (WALDMANN et al., 1961; SCHMIDT and RIEMANN, 1980), dogs (CAMPBELL et al., 1968; BURNS, 1982; FOSSUM et al., 1987; SUTER et al., 1987; FOSSUM et al., 1990; KLEINT, 1994; WILLARD et al., 2000), cattle (NIELSON and ANDERSEN, 1967) and in non-human primates (RODGER et al., 1980), that results in malabsorption (RILEY and TURNBERG, 1993). Intestinal lymphangiectasia is the most common lesion associated with protein-losing enteropathy in dogs. Protein-losing enteropathy occurs in association with numerous gastrointestinal and systemic disorders, including idiopathic inflammatory enteropathies (lymphocytic-plasmacytic, eosinophilic, or granulomatous gastroenteritis), gastrointestinal neoplasia, foreign bodies, intussusceptions, small intestinal bacterial overgrowth (SIBO), systemic lupus erythematosus (SLE), disorders of the intestinal hemolymphatic system, portal hypertension, gastrointestinal parasitism (giardiasis), fungal enteropathies, acute infectious (viral or bacterial) enteritis (MATTHEEUWS et al., 1974; BURNS, 1982; VAN KRUININGEN et al., 1984; WILLIAMS, 1996; WILLARD, 2001). Intestinal lymphangiectasia is characterized by obstruction and dysfunction of the intestinal lymphatic network. Lymphatic obstruction leads to stasis of chyle within dilated lacteals and lymphatics of the bowel wall and mesentery. Over distended lacteals release intestinal lymph into the intestinal lumen (loss of lymphatic contents - plasma proteins, lymphocytes and chylomicrons) either by extravasation or by rupture (HALL and SIMPSON, 2000). The functional consequences of lymphangiectasia are hypoproteinemia, lymphocytopenia, hypocholesterolemia, hypocalcemia and fat malabsorption (BURROWS et al., 1995; TAMS, 1996).

Lymphangiectasia can result from a number of causes. Primary or congenital lymphangiectasia is the result of insufficiency or aplasia of lymphatic vessels. In secondary or acquired intestinal lymphangiectasia functional obstruction of the lymphatics develops secondary to the condition, such as right-side heart failure, constrictive heart disease, intestinal neoplasia and inflammation (SCHMIDT and RIEMANN, 1980; RIEMANN and SCHMIDT, 1981; BURNS, 1982; HOLLAND, 1997). Generalized inflammatory disease of the intestinal lymphatic network is probably the most common factor in pathogenesis of the disease. The cause of this

inflammation is undetermined in most cases (BURROWS et al., 1995; WILLIAMS, 1996; WILLARD et al., 2000).

Breed predilections for intestinal lymphangiectasia are not documented, although familial tendency for protein-losing enteropathy has been reported in soft-coated wheaten terriers, Yorkshire terriers, basenjis, Rottweilers and lundehunds. The mode of inheritance is unknown. Mean age is 5 years and age range is 2-9 years (HOLLAND, 1997).

Clinical signs are variable. Chronic intermittent or persistent light-coloured diarrhoea of a watery to semi-solid consistency may be observed. Some dogs may present only ascites and edema. Excessive enteric loss of plasma proteins in lymphangiectasia leads to hypoalbuminemia and reduced plasma oncotic pressure. This in turn results in edema and effusion. Presenting signs include dependent pitting edema of subcutis and limbs, ascites, and hydrothorax that can lead to respiratory distress. Sporadic vomiting and lethargy have also been reported, but vomiting is not a feature of lymphangiectasia. Weight loss and progressive emaciation are commonly associated with longstanding protein-losing enteropathy (BURROWS et al., 1996; TAMS, 1996; HOLLAND, 1997a).

The aim of this paper is to present a case of secondary intestinal lymphangiectasia in a dog in Croatia.

Materials and methods

A 5-year-old male golden retriever was presented at the Clinic for Internal Diseases, Faculty of Veterinary Medicine, University of Zagreb. The dog was fully clinically examined, which also included laboratory examinations. Thoracic and abdominal radiographs were also taken.

Blood samples were taken for hematologic and biochemical analysis. Hematologic analysis was performed using hematologic counter Baker System Serrono 9120 CP (Serrono-Baker Diagnostic, INC., 100 Cascade Drive, Allentown, Pennsylvania 18103, U.S.A.) Biochemical analysis was performed after centrifugation at 1200 g for ten minutes. Creatinine, blood urea nitrogen (BUN), glucose, total serum proteins, bilirubin, calcium, cholesterol, triglyceride levels and activity of alanine aminotransferase

(ALT), aspartate aminotransferase (AST), serum amylase and creatine kinase were measured using biochemical autoanalyser Technicon RA 1000 (Technicon Instruments Corporation, New York, U.S.A.) Reagents were supplied by Randox (Randox Laboratories Ltd., United Kingdom).

Therapy lasted for 14 days and consisted of metronidazole (20 mg/kg bid), prednisone (1mg/kg bid). Dietary therapy involved feeding a low-fat diet with an ample supply of high quality protein. Due to the unchanged health status of the patient during treatment, the dog was euthanised at the owner's request.

A complete necropsy was carried out. Tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 3-5 ěm and stained with haematoxylin end eosin.

Results

A 5-year-old male Golden retriever was presented with chronic intermittent diarrhoea and occasional vomiting with weight loss. The patient was under therapy (amoxicillin, ranitidine) at a private clinic, but without any improvement in the health status.

Table 1. Results of hematologic findings in a 5-year-old male Golden retriever with secondary intestinal lymphangiectasia

Complete blood count	Values	KRAFT and DÜRR (1997)
RBC (x 10^{12} /L)	5.79	5.5-8.5
Hemoglobin (g/L)	151	150-190
PCV (%)	45.6	44-52
MCV (fL)	76	60-77
WBC (x 10^{9}/L)	17.8	6-15
Neutrophils (%)	92	55-75
Bands (%)	0	0-4
Lymphocytes (%)	3	13-30
Monocytes (%)	4	0-4
Basophils	0	0-1
Eosinophils (%)	1	0-6

Clinical examination at the Clinic for Internal Disease, Faculty of Veterinary Medicine, revealed ascites and pleural effusion, which was radiographically confirmed. At contrast radiographic examination of the gastrointestinal tract revealed severe duodenitis and jejunitis with flaky, rough mucosa.

Hematologic examination revealed mild leucocytosis and strong lymphocytopenia (Table 1). Biochemical findings showed hypocholesterolemia, panhypoproteinemia (hypoalbuminemia) and hypocalcemia (Table 2).

Table 2. Serum biochemistry values in a 5-year-old male Golden retriever with secondary intestinal lymphangiectasia

Serum biochemistry	Values	KRAFT and DÜRR (1997)
Alanine aminotransferase (U/L)	39	up to 55
Aspartate aminotransferase (U/L)	16	up to 25
Bilirubin (μmol/L)	2.2	up to 3.4
Creatine kinase (U/L)	18	up to 90
Creatinine (μmol/L)	80	35-106
Blood urea nitrogen (mmol/L)	4.2	3.3-8.3
Protein (total) (g/L)	35	54-75
Albumin (g/L)	18	25-44
Cholesterol (mmol/L)	1.63	3.1-10.1
Triglyceride (mmol/L)	0.58	0.29-3.88
Calcium (mmol/L)	1.9	2.3-3.0
Amylase (U/L)	431	up to 1650
Glucose (mmol/L)	4.6	3.1-6.7

At necropsy, the mesenteric lymphatic vessels were firm, dilated and contained a milky fluid. Small intestines of the dog were dilated and filled with soft to watery, greenish to yellow faeces. Mucosa of the small intestines was thickened by edema. The villi of the mucosa were white and clearly

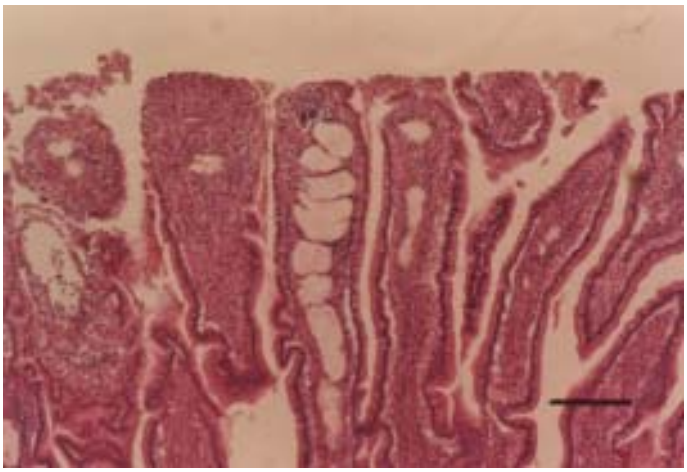

Fig. 1. Dilated lacteals of the small intestinal villi. H&E; ×25; scale bar = 150 μm.

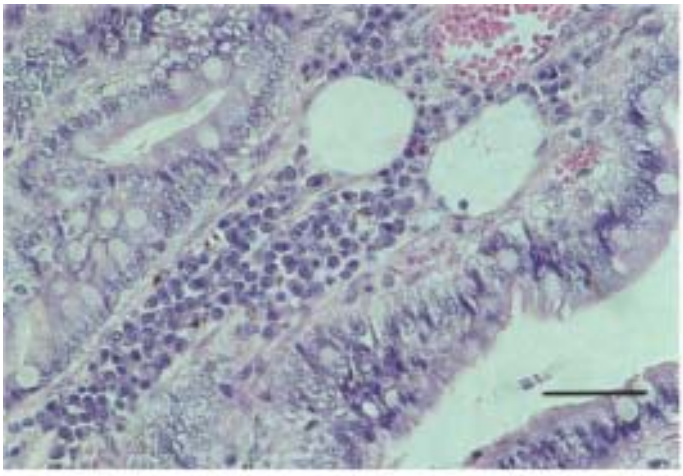

Fig. 2. Intense mononuclear, particularly plasma cells infiltrations and mild edema of the lamina propria. H&E; ×100; scale bar = 50 μm.

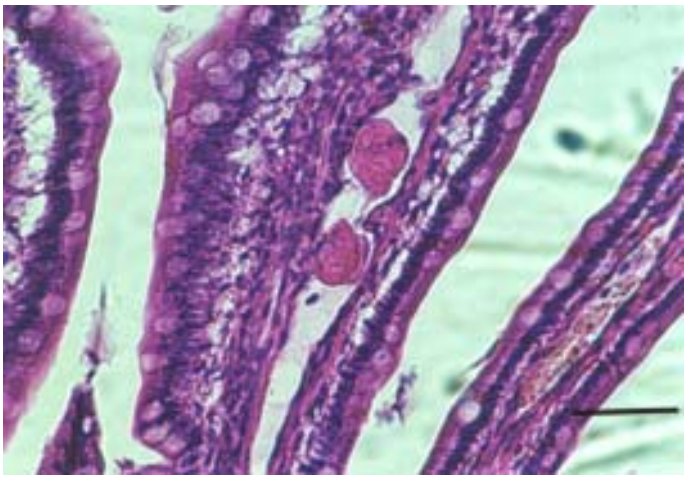

Fig. 3. Eosinophilic material in the lacteal of the intestinal villi. H&E; ×100; scale bar = 50 μm.

macroscopically visible. Multiple white firm nodules up to 5 mm in diameter were located at the mesenteric border of the small intestine and appeared extended into the tunica muscularis.

The pleural cavity contained approximately 150 ml of clear, pale yellow, watery fluid, and abdominal cavity contained approximately 300 ml of similar fluid.

Microscopically the duodenum and jejunum were most severely affected. Severe multifocal lymphangiectasia was observed in the small intestines. The lacteals in the villi were dilated, particularly in the tips. (Fig. 1). The tips of most villi were large, club-like, with an intense mononuclear particularly plasma cells infiltrations and mild edema of the lamina propria (Fig. 2). Many lacteals in villi were filled with eosinophilic material and occasional lymphocytes (Fig. 3). Edema of the submucosa and muscularis and dilatation of their lymphatic vessels in the small intestines were present (Fig. 4). The walls of mesenterial artery were infiltrated with mononuclear cells (Fig. 5), while some lymphatic vessels were completely obturated by mononuclear cells and forming granulomas (Fig. 6).

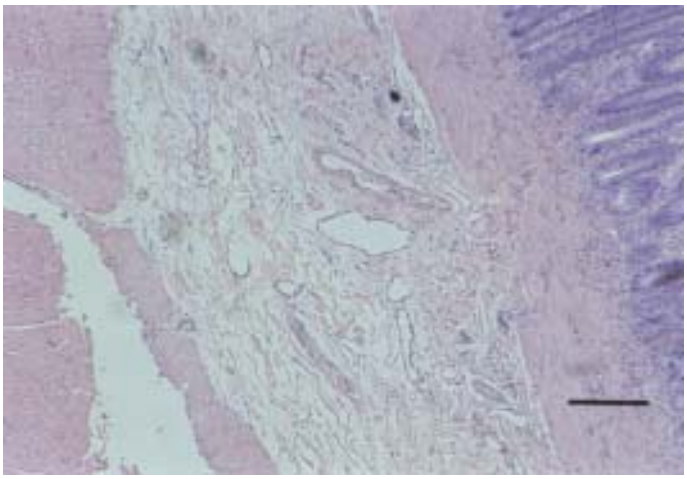

Fig. 4. Submucosal edema and dilation of the submucosal lymphatic vessels in the small intestines. H&E; ×25; scale bar = 150 μm.

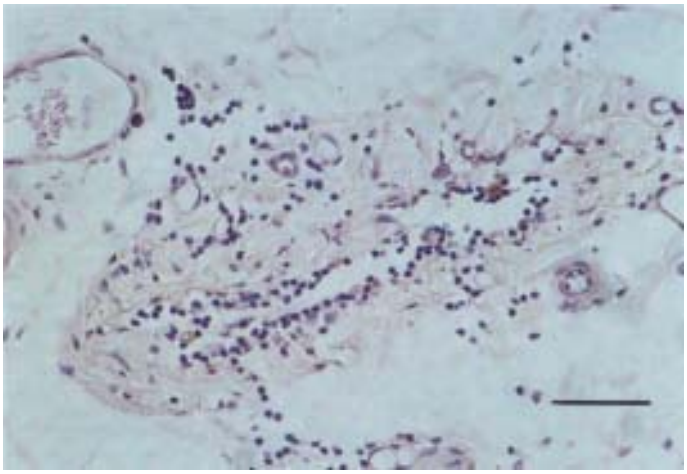

Fig 5. The wall of the mesenterial artery, infiltrated with mononuclear cells. H&E; ×50; scale bar = 100 μm.

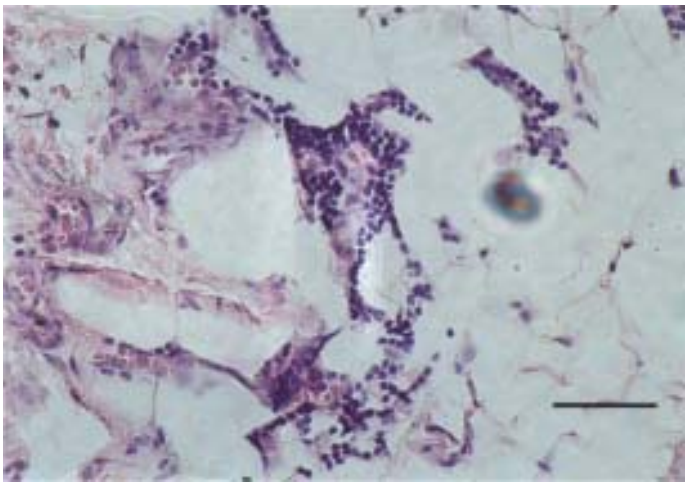

Fig. 6. Mesenterial lymphatic vessel was completely obturated by mononuclear cells and forming granuloma. H&E; ×50; scale bar = 100 μm.

Discussion

Protein-losing enteropathy is caused by obstruction and dysfunction of gastrointestinal lymphatic tissue and leads to malabsorption in dogs (BURNS, 1982; FOSSUM et al., 1987; SUTER et al., 1987; BURROWS et al., 1995). The most important protein-losing gastroenteropathies are associated with chronic inflammatory diseases and circulatory diseases such as lymphangiectasia (WILLIAMS, 1996).

The disease is commonly diagnosed in 5-year-old dogs, as was the case with our patient (HOLLAND, 1997).

Clinical signs involved chronic diarrhoea, occasional vomiting, ascites and occasional dyspnea due to pleural effusion. Substantial weight loss and progressive cachexia was noticed. Clinical findings were correlated with literature data as symptoms of lymphangiectasia (RILEY and TURNBERG, 1993; BURROWS et al., 1995; TAMS, 1996; WILLIAMS, 1996; HOLLAND, 1997).

Biochemical findings revealed severe reduction of protein (35g/L) and albumin levels (18 g/L) in blood serum which lead to ascites and pleural

effusion (TAMS, 1996; WILLIAMS, 1996; HOLLAND, 1997). When severe panhypoproteinemia is present, an underlying hemolymphatic disease or circulatory diseases are usually responsible rather than chronic inflammatory diseases. Conversely, when loss of plasma proteins is, by protein-losing gastroenteropathy, due to inflammation, there are often associated clinical signs of gastrointestinal disease such as vomiting, anorexia or diarrhoea which suggest an underlying problem in the gastrointestinal tract (WILLIAMS, 1996; WILLARD, 2001). Cholesterol (1.63 mmol/l) and calcium (1.9 mmol/l) levels were also decreased. Hypocalcemia is a common finding in patients suffering from lymphangiectasia, due to loss of proteins which are calcium binders (BURROWS et al., 1995). Hematological findings revealed severe lymphocytopenia (3%), which is a common laboratory finding, along with low protein, albumin, cholesterol and calcium levels in dogs suffering from lymphangiectasia (TAMS, 1996; WILLARD, 2001).

The above-mentioned clinical findings presented a solid base for assuming a case of secondary intestinal lymphangiectasia.

Pathoanatomical examination revealed white nodules about 5 mm in diameter in intestinal subserosis and along the mesenterium that correspond to lymphangitis granulomatosa in literature data (VAN KRUININGEN et al., 1984; MESCHTER et al., 1987; HALL and SIMPSON, 2000). Lipogranulomatous lymphangitis is sometimes reported in association with lymphangiectasia, but it is not clear which is the primary event; lymphangitis could cause lymphatic obstruction, or leakage of lymph could cause granuloma formation (HALL and SIMPSON, 2000). Macroscopically obvious white intestinal villi of the small intestines mucosa confirmed the clinical diagnosis (CAMPBELL et al., 1968; MATTHEEUWS et al., 1974; BURNS, 1982; VAN KRUININGEN et al., 1984; FOSSUM et al., 1987; MESCHTER et al., 1987). Dilated lacteals of the small intestinal villi and lymphatics of the small intestinal mucosa dominated in histopathological findings, which also confirmed clinical and pathoanatomical diagnoses (CAMPBELL et al., 1968; MATTHEEUWS et al., 1974; BURNS, 1982; VAN KRUININGEN et al., 1984; FOSSUM et al., 1987; MESCHTER et al., 1987; FOSSUM et al., 1990; KLEINT, 1994; WILLARD et al., 2000). Focal infiltration of lamina propria with mononuclear cells, particularly plasma cells and mild edema of lamina propria, was also in correlation

with literature data (FOSSUM et al., 1987; MESCHTER et al., 1987; SUTER et al., 1987; HALL and SIMPSON, 2000). Also, in our case report many lacteals in villi were filled with eosinophilic material and occasional lymphocytes; that fact that edema of the submucosa and muscularis and dilatation of their lymphatic vessels in the small intestines were present was also in correlation with literature data (FOSSUM et al., 1990; KLEINT, 1994; HOLLAND, 1997; HALL and SIMPSON, 2000). For a definitive diagnosis, ballooning dilatation of lymphatics must be evident not only in the mucosa but also in the submucosa. Assessment of the degree of inflammatory cell infiltrate in the lamina propria is subjective, and if there is edema the density of cells may be underestimated (HALL and SIMPSON, 2000). Secondary lymphangiectasia in our patient could be because of the lymphangitis or inflammatory bowel disease. According to literature data secondary lymphangiectasia due to lymphangitis and consequent occlusion with granulomas of mesenterial lymphatics lead to dilatation of lymphatics and lacteals of the intestines (VAN KRUININGEN et al., 1984; MESCHTER et al., 1987). The result was loss of proteins and development of ascites and pleural effusion. Also, the problem is that true lymphangiectasia must be distinguished from secondary dilatation of lacteals sometimes noted in inflammatory bowel disease (HALL and SIMPSON, 2000). The cause of mononuclear lymphangitis remains to be discovered through further analysis.

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SAŽETAK

U radu je iscrpno prikazana klinička i patološkomorfološka slika limfangiektazija u psa. Životinja je dovedena na Kliniku za unutarnje bolesti Veterinarskog fakulteta u Zagrebu zbog kroničnog proljeva i progesivnog mršavljenja. Nakon provedene temeljite kliničke i biokemijske pretrage nalazi su upućivali na enteropatiju zbog gubitka proteina uzrokovanu limfangiektazijom. U skladu s nalazima provedena je odgovarajuća terapija, koja nije davala zadovoljavajuće rezultate, pa je na zahtjev vlasnika životinja eutanazirana. Patoanatomskom i patohistološkom pretragom potvrđena je sekundarna limfangiektazija koja može biti rezultat mononuklearnog limfangitisa nepoznate etiologije, a može biti potaknuta i upalnom crijevnom bolesti.

Ključne riječi: pas, enteropatija, limfangiektazija, limfangitis, patološki nalaz