J. Comp. Path. 2018, Vol. 160, 39–49

Available online at www.sciencedirect.com

ScienceDirect

ELSEVIER

www.elsevier.com/locate/jcpa

SPONTANEOUSLY ARISING DISEASE

Small Intestinal Lymphatic Hypoplasia in Three Dogs with Clinical Signs of Protein-losing Enteropathy

J. M. Malatos*, N. A. Kurpios† and G. E. Duhamel*

** Department of Biomedical Sciences, New York Animal Health Diagnostic Center and † Department of Molecular Medicine, College of Veterinary Medicine, Cornell University, Ithaca, New York, USA*

Summary

Intestinal lymphatic hypoplasia (ILH) is a rare but well-documented cause of protein-losing enteropathy (PLE) in human infants. To our knowledge, this condition has not been reported previously in veterinary medicine. Here we report the clinical and histopathological findings in three dogs that presented with clinical signs of PLE. The onset of PLE was early in an 18-month-old Great Pyrenees, while the other two dogs, a pug and a Tibetan terrier, had a later onset at 4 and 12 years of age, respectively. The presence of intestinal lymphatic and blood vessels was assessed by immunohistochemistry for human prospero homeobox 1 (prox-1), a lymphatic endothelial nuclear transcription factor and human von Willebrand factor (vWf), a marker of vascular endothelial cells, respectively. Small intestinal specimens taken from each dog showed severe mucosal oedema with a lack of prox-1 labelling of villous lacteals, dilated and tortuous vWf immunoreactive villous arterial and capillary blood vessels, and variable lamina propria mixed inflammatory cell infiltrates. Other histological features of ILH included club-shaped villi that were lined by low cuboidal epithelium or epithelial cells with cytoplasmic pallor and microvacuolar change, extrusion zone epithelial inversion and thin and inconspicuous villous longitudinal smooth muscles. While ILH is an uncommon diagnosis, it should be considered as a differential in dogs with clinical signs of PLE. The cause of canine ILH is unknown; however, a congenital abnormality with early or late onset of clinical signs is suspected. Diagnosis of ILH can be challenging; however, immunohistochemical labelling of lymphatic endothelial cells with prox-1 is essential for making this diagnosis.

Keywords: dog; intestinal lymphatic hypoplasia; lacteal; lymphatics

Introduction

Protein-losing enteropathy (PLE) is a clinical condition characterized by net loss of protein from the gastrointestinal tract resulting in hypoalbuminaemia, ascites, pleural and pericardial effusions and growth retardation from malnutrition (Waldmann, 1966). The loss of albumin in patients with PLE is primarily from the small intestine and is clinically significant when the loss exceeds the synthetic rate of the liver, which in man, can compensate at up to twice the normal rate (Waldmann, 1966). There are several well-known causes of PLE in dogs; however, intestinal lymphatic obstruction, characterized by intestinal lymphangiectasia (IL), is one of the most common causes, particularly in certain breeds of dog including the Yorkshire terrier, soft-coated wheaten terrier, Lunderhund and Basenji (Van Kruiningen *et al.*, 1984; Peterson and Willard, 2003; Dossin and Lavoué, 2011; Simmerson *et al.*, 2014). Another clinical condition associated with PLE, first recognized by Willard *et al.* (2000), is characterized by ectatic intestinal crypts, primarily within the duodenum (Peterson and Willard, 2003; Dossin and Lavoué, 2011; Simmerson *et al.*, 2014). The

Correspondence to: G.E. Duhamel (e-mail: ged36@cornell.edu).

0021-9975/$ - see front matter
https://doi.org/10.1016/j.jcpa.2018.02.005

Table 1
Clinical history of dogs with intestinal lymphatic hypoplasia

Case	*Location*	*Breed*	*Age*	*Sex*	*Clinical signs at presentation and outcome*
1	Maryland	Great Pyrenees	1.5 y	F	Inappetence, chronic vomiting and diarrhoea, weight loss/ humanely destroyed 45 days after biopsy
2	New York	Pug	4 y	M	Limping, ventral torso and hindlimb pitting oedema, diarrhoea/ humanely destroyed 20 days after biopsy
3	New York	Tibetan terrier	12 y	M	Inappetence, chronic vomiting and diarrhoea, weight loss/ humanely destroyed 14 days after biopsy

y, years; F, female; M, male.

pathogenesis and mechanism of multifocal crypt ectasia resulting in PLE remains poorly understood. With IL, hypoalbuminaemia is attributed to loss of lymph into the lumen of the intestine; however, dogs with IL can also show decreased lymphocyte count, hypocholesterolaemia, hypocalcaemia and hypomagnesaemia (Simmerson *et al.*, 2014).

Intestinal lymphatic hypoplasia (ILH) is a rare, but well-documented cause of PLE in human infants (Hardikar *et al.*, 1997). Although ILH has been associated with PLE, the role of lymphatic hypoplasia in the pathogenesis of PLE is uncertain (Hardikar *et al.*, 1997; Storman *et al.*, 2002). Here we present the clinical and histopathological findings in intestinal specimens taken from three dogs that presented with clinical signs of PLE and histological evidence of ILH. To our knowledge, ILH has not been previously reported in veterinary medicine and this is the first description of the spontaneously arising disease in animals.

Materials and Methods

Case Material

The signalment, clinical presentation and serum biochemistry values of three dogs investigated in the present study are presented in Tables 1 and 2. Dog 1 was presented when 18 months old to a referral internal medicine specialist with a 3-month history of chronic vomiting, diarrhoea, inappetence, poor body condition (about half the size of a breed and age-matched animal) and persistent hypoproteinaemia. Approximately 3 months earlier, a routine health check examination had revealed a low serum albumin and low resting cortisol (see Table 2).

Two months later, the dog was presented to a second veterinary clinic with a 3-week history of decreased appetite, lethargy and watery diarrhoea. At that time, an adrenocorticotropic hormone (ACTH) stimulation test revealed low, but normal values and the dog was prescribed two doses of dexamethasone sodium phosphate (0.5 mg q12 h) transitioned to prednisone (10 mg q24 h), metronidazole (375 mg q12 h), a proton pump inhibitor (pantoprazole) transitioned to omeprazole (30 mg q24 h), a broad-spectrum dewormer (Drontal Plus, Bayer, Shawnee Mission, Kansas, USA) and a bland diet. Appetite improved; however, vomiting and diarrhoea persisted and approximately 5 days later the dog was presented to a third veterinary clinic where haematological and serum biochemical evaluations revealed leukocytosis (24.79×10^9/l; reference interval $5.05–16.76 \times 10^9$/l) with neutrophilia (19.26×10^9/l; reference interval $2.95–11.64 \times 10^9$/l), low normal albumin (24 g/l; reference interval 23–40 g/l) and hypocholesterolaemia (1.45 mmol/l; reference interval 2.85–8.29 mmol/l. Abdominal radiographs revealed a distended stomach and because of concerns for a possible intestinal obstruction, an exploratory laparotomy was performed. At surgery, 1.2 l of ingesta and a large grass bolus were removed from

Table 2
Selected serum biochemistry values of dogs with intestinal lymphatic hypoplasia

Case	*Urea*	*Creatinine*	*Total protein*	*Albumin*	*Calcium*	*Magnesium*
	mmol/l	*mmol/l*	*g/l*	*g/l*	*mmol/l*	*mmol/l*
1A	6.43	0.08	27	12	2.05	ND[b]
1B	9.28	0.07	37	16	2.07	ND
1C	5.71	0.05	38	18	2.17	ND
2	3.93	0.06	33	4	1.95	ND
3	6.07	0.06	33	12	1.90	0.66
Reference interval	3.21–11.07	0.04–0.11	55–75	23–40	2.10–2.94	0.74–0.99

Time of blood sample collection: 1A, 27 days before biopsy; 1B, 2 days before biopsy; 1C, day of humane destruction; 2, 7 days before biopsy; 3, 4 days before biopsy; ND, not determined.