

Intestinal Leiomyositis: A Cause of Chronic Intestinal Pseudo-Obstruction in 6 Dogs

A.C. Zacuto, P.A. Pesavento, S. Hill, A. McAlister, K. Rosenthal, O. Cherbinsky, and S.L. Marks

Background: Intestinal leiomyositis is a suspected autoimmune disorder affecting the muscularis propria layer of the gastrointestinal tract and is a cause of chronic intestinal pseudo-obstruction in humans and animals.

Objective: To characterize the clinical presentation, histopathologic features, and outcome of dogs with intestinal leiomyositis in an effort to optimize treatment and prognosis.

Animals: Six client-owned dogs.

Methods: Retrospective case series. Medical records were reviewed to describe signalment, clinicopathologic and imaging findings, histopathologic diagnoses, treatment, and outcome. All biopsy specimens were reviewed by a board-certified pathologist.

Results: Median age of dogs was 5.4 years (range, 15 months–9 years). Consistent clinical signs included vomiting (6/6), regurgitation (2/6), and small bowel diarrhea (3/6). Median duration of clinical signs before presentation was 13 days (range, 5–150 days). Diagnostic imaging showed marked gastric distension with dilated small intestines in 4/6 dogs. Full-thickness intestinal biopsies were obtained in all dogs by laparotomy. Histopathology of the stomach and intestines disclosed mononuclear inflammation, myofiber degeneration and necrosis, and fibrosis centered within the region of myofiber loss in the intestinal muscularis propria. All dogs received various combinations of immunomodulatory and prokinetic treatment, antimicrobial agents, antiemetics, and IV fluids, but none of the dogs showed a clinically relevant improvement with treatment. Median survival was 19 days after diagnosis (range, 3–270 days).

Conclusions and Clinical Importance: Intestinal leiomyositis is a cause of intestinal pseudo-obstruction and must be diagnosed by full-thickness intestinal biopsy. This disease should be considered in dogs with acute and chronic vomiting, regurgitation, and small bowel diarrhea.

Key words: Ileus; Intestine; Muscularis; Obstruction; Stomach.

Chronic intestinal pseudo-obstruction (CIPO) is a well-documented syndrome in humans and refers to impaired intestinal motility that results in clinical signs of obstruction without evidence of mechanical occlusion of the intestinal lumen.¹ The disease is uncommonly reported in veterinary medicine, although it has been reported in several species including dogs, horses, cats, and birds.^{2–11} Pseudo-obstruction repre-

Abbreviations:

ACTH	adrenocorticotropic hormone stimulation test
CIPO	chronic intestinal pseudo-obstruction
CT	computed tomography
GFAP	glial fibrillary acidic protein
GI	gastrointestinal
IHC	immunohistochemistry stain
Spec cPL	canine pancreatic-specific lipase
SIBO	small intestinal bacterial overgrowth
VMTH	Veterinary Medical Teaching Hospital
GMS	Grocott's methenamine silver stain
PAS	periodic acid–Schiff stain

From the William R. Pritchard Veterinary Medical Teaching Hospital, University of California, Davis, (Zacuto); Department of Pathology, Microbiology, and Immunology, School of Veterinary Medicine, Davis, (Pesavento); Veterinary Specialty Hospital, San Diego, (Hill); PETS Referral Center, Berkeley, CA (McAlister); Westside Veterinary Center, New York, NY (Rosenthal); Atascadero Pet Hospital & Emergency Center, Atascadero, (Cherbinsky); Department of Medicine & Epidemiology, School of Veterinary Medicine, Davis, CA (Marks).

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Corresponding author: Dr S.L. Marks, Department of Medicine & Epidemiology, School of Veterinary Medicine, University of California, Davis, One Shields Avenue, Davis, CA 95616; e-mail: slmarks@ucdavis.edu.

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sents the most severe form of motility disorders, and its cause may be congenital or acquired, with further classification into primary (idiopathic) or secondary disorders.¹ Several causes of secondary pseudo-obstruction have been subclassified into developmental, infectious, inflammatory, auto-immune, metabolic, paraneoplastic, endocrine, and toxic etiologies in the human medical literature.^{1,12,13} The most common form of this disorder in humans is idiopathic in nature, but intestinal dysfunction sometimes is attributed to an autoreactive T-cell response.^{14,15} Regardless of causation, CIPO is histologically classified into myopathic, mesenchymopathic, and neuropathic groups.¹

Leiomyositis affects contractility of the enteric smooth muscle cells because of infiltration of lymphocytes between functional myocytes, causing subsequent ileus.¹⁴ Affected humans and dogs present with marked gastric and small intestinal dilatation with severe hypomotility, resulting in clinical signs of abdominal discomfort, vomiting, regurgitation, diarrhea, anorexia, and weight loss of vari-

able onset.^{2-8,12,15} The syndrome has been poorly defined in dogs to date, and all but 1 of the publications in the peer-reviewed veterinary literature are single-case reports.²⁻⁸ The prognosis of dogs with intestinal leiomyositis generally is poor with survival times ranging from 10 days to 5 weeks after diagnosis.^{5,6} In addition, management of CIPO in people is extremely challenging and is predominantly aimed at controlling symptoms and minimizing complications. Earlier recognition of the disease and aggressive nutritional and medical management are associated with an improved prognosis, fewer surgical procedures, and prolonged survival into adulthood.^{1,12}

The objective of this study was to comprehensively review the clinical, diagnostic, and histopathologic findings of 6 dogs diagnosed with intestinal leiomyositis. In addition, the diagnostic and management strategies and clinical outcome of affected dogs were evaluated in an effort to optimize the prognosis of dogs with this poorly understood disorder.

Materials and Methods

Criteria for Selection of Dogs

A comprehensive search of the William R. Pritchard Veterinary Medical Teaching Hospital (VMTH) Medical Record database was performed between April 2006 and October 2014 for dogs with clinical signs and radiographic or ultrasonographic features consistent with intestinal obstruction without evidence of mechanical occlusion of the intestinal lumen. In addition, all dogs had full-thickness gastrointestinal biopsies indicative of intestinal leiomyositis. The dogs that were included from 3 privately owned veterinary practices between April 2014 and March 2015 had the same inclusion criteria as those included from the William R. Pritchard VMTH, and were included after telephone consultations initiated by the practitioners with 1 of the authors (SLM).

Procedure

Information available on the 6 dogs included signalment, presenting complaint, physical examination findings, clinical laboratory results, abdominal imaging and surgical reports, and clinical outcomes. Endoscopic reports were available for 1/6 dogs. Full-thickness biopsy specimens, necropsy results, or both from all dogs were regular submissions to either the Anatomic Pathology service at UC Davis or were forwarded to that service by a reference laboratory. Tissues were fixed in 10% neutral buffered formalin, embedded routinely in paraffin wax, and 5- μ m sections were stained with hematoxylin and eosin (H&E), trichrome, or processed for immunohistochemistry using antibodies against alpha smooth muscle actin,^a CD3,^b CD20,^c CD18,^d CD79,^e glial fibrillary acidic protein^f (GFAP), or neuron-specific enolase.^g Histopathology and immunohistochemistry were evaluated by a single board-certified pathologist (PP).

Results

All dogs were client-owned animals and were evaluated at the VMTH at UC Davis or 3 other privately owned veterinary hospitals.

Signalment

Breeds represented included Labrador Retriever (dog 1), Labrador Retriever mix (dog 2), Bernese Mountain

Dog (dog 3), Portuguese Water Dog (dogs 4 and 5), and a German Shorthaired Pointer (dog 6). The median age at the time of diagnosis was 5.4 years (range, 15 months–9 years).

History and Presenting Signs

History of all dogs included vomiting (6/6), small bowel diarrhea (3/6), regurgitation (2/6), and anorexia (2/6). Owners reported no appreciable weight loss in 5 of the 6 dogs. The median duration of clinical signs for all dogs before presentation was 13 days (range, 5–150 days). None of the dogs had a previous history of gastrointestinal disease.

Physical Examination

Physical examination abnormalities included abdominal discomfort (3/6 dogs) and dehydration (2/6 dogs). All of the dogs were normothermic at presentation. Dog 1 displayed signs of increased respiratory effort and protrusion of its nictitating membrane bilaterally. None of the dogs had evidence of borborygmi on physical examination or of distended intestinal loops. Median body weight was 30.4 kg (range, 19.7–38.7 kg). Body condition scores ranged from 3/9 to 6/9 (median, 5/9).

Clinicopathologic Data

Complete blood count and serum biochemistry results were available on all 6 dogs, and results are presented in Table 1. No dogs were anemic on presentation, and 2 dogs had a mild to moderate neutrophilia (14,300 cells/ μ L and 23,983 cells/ μ L, respectively; reference range, 3000–10,500 cells/ μ L). Mild hypoalbuminemia was present in dogs 1 and 3 (3.1 g/dL and 3.3 g/dL; reference range, 3.4–4.3 g/dL), and none of the dogs were panhypoproteinemic. Hypocholesterolemia was present in dog 2 (87 mg/dL; reference range, 139–353 g/dL). Serum cobalamin concentration was available in 2/6 dogs, and one of the dogs was hypocobalaminemic (201 ng/L; reference range, 271–875 ng/L). Adrenocorticotropic hormone stimulation tests were performed in 3/6 dogs, and all of the results were unremarkable. A Spec cPL^h test was performed in 4/6 dogs, and results ranged from 50 to 394 μ g/dL (median, 255.5 μ g/dL; reference range, 201 to 399 μ g/L is questionable range for canine pancreatitis; >400 μ g/L is consistent with pancreatitis).

Diagnostic Imaging

Abdominal radiographs were performed in 4/6 dogs (dogs 1, 3, 5, and 6), of which 3 dogs had abnormal findings characterized by marked gastric distension with segmentally to diffusely dilated small intestines. Radiographs on dog 5 were unremarkable, and radiographs on dog 6 were interpreted as a small intestinal mechanical obstruction. Diffuse dilatation of the small and large intestine with functional ileus was diagnosed in the other 2 dogs (dogs 1 and 3; Fig 1). Pre-operative

Table 1. Results of laboratory parameters evaluated in dogs with intestinal leiomyositis.

Laboratory Parameter	Number of Dogs Tested	Median	Range	Reference Interval
Cobalamin	2/6	243.5 ng/L	201–286 ng/L	271–875 ng/L
Pre-ACTH	3/6	4.1 µg/dL	1.7–8.7 µg/dL	0.0–6.0 µg/dL
Post-ACTH	2/6	20 µg/dL	12.8–27.3 µg/dL	0.0–6.0 µg/dL
Spec cPL	4/6	255.5 µg/L	50–394 µg/L	>400 µg/L
Albumin	6/6	3.4 g/dL	3.1–3.9 g/dL	3.4–4.3 g/dL
Globulin	6/6	2.8 mg/dL	2.2–3.3 mg/dL	1.7–3.1 mg/dL
Cholesterol	6/6	179 mg/dL	87–221 mg/dL	139–353 mg/dL
Hematocrit	6/6	45.5%	37–50%	30–50%
Leukocytes	6/6	11,145 cells/µL	7,100–27,130 cells/µL	6,000–13,000 cells/µL
Neutrophils	6/6	8,084 cells/µL	4,544–23,983 cells/µL	3,000–10,500 cells/µL
Monocytes	6/6	1,022 cells/µL	630–1,716 cells/µL	150–1,200 cells/µL

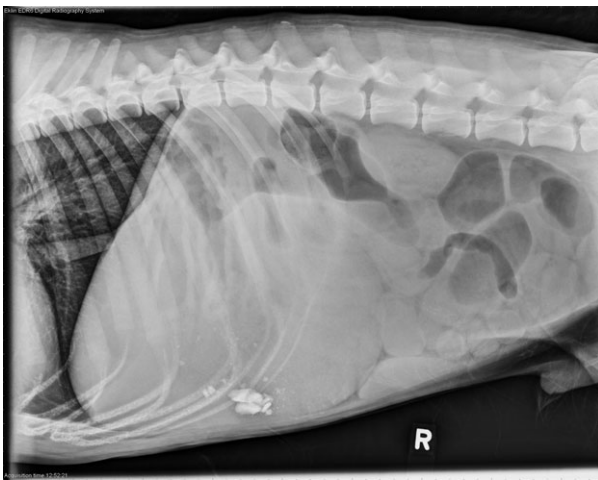


Fig 1. Right lateral survey radiograph obtained from a 2-year MC Bernese mountain dog (dog 3). There is severe dilatation of the stomach with fluid and a small volume of gas. There are multiple irregular, variably sized mineral opacities present within the lumen of the stomach. The small bowel and colon is diffusely and severely fluid and gas dilated. Apparent gravel sign in the stomach is most consistent with chronic gastric outflow obstruction; however, given the diffuse changes, an underlying functional ileus should be considered.

thoracic radiographs were obtained in 3/6 dogs, and were abnormal in one of these dogs. Dog 1 had a moderate interstitial to alveolar pattern in all dependent lung lobes, consistent with aspiration pneumonia, and fluid was detected in the caudal esophagus.

Abdominal ultrasound examinations were performed in 5/6 dogs (dogs 1, 2, 4, 5, and 6), all of which showed poor to absent peristalsis with segmentally to diffusely dilated small intestines. Dog 3 did not have an abdominal ultrasound examination performed because of high suspicion for a jejunal foreign body and the pursuit of an enterotomy. No evidence of overt mechanical obstruction was appreciated in that dog during its surgery. Intraluminal debris concerning for foreign material was noted in 3/6 dogs (dogs 2, 5, and 6) during their abdominal ultrasound examinations. Dogs 4 and 6 had loss of gastric and jejunal wall layering. Dog 6 also was noted to have a scant amount of free abdominal

fluid. Other findings included a diffusely hypoechoic liver in dog 1, hypoechoic pancreas with hyperechoic mesentery in dog 4 (Spec cPL^h not performed), and mild mesenteric lymphadenopathy in dog 6. Dog 1 had a laparotomy performed at 1 of the 3 private practices for a suspected gastrointestinal mechanical obstruction 5 days before presentation at UC Davis. Full-thickness gastrointestinal biopsies were acquired from the dog at that time. A computed tomography (CT) scan of the dog's abdomen was performed at UC Davis 11 days postoperatively after assessment of the dog's ultrasound procedure and based on the surgeon's concern for potentially missing a gastrointestinal foreign body. The CT scan showed multiple, dilated, fluid-filled loops of the bowel, and fluid dilatation of the stomach, consistent with functional ileus. In addition, the jejunal wall appeared thickened and there was evidence of suspected postoperative adhesions without evidence of obstructive disease in the dog.

Endoscopy and Laparotomy

An exploratory laparotomy for a suspected mechanical obstruction was performed on dog 1 5 days before referral to UC Davis, and full-thickness intestinal biopsies were obtained during the laparotomy. Histopathologic diagnosis at a reference laboratory was moderate lymphocytic–plasmacytic enteritis, but upon referral to UC Davis, a diagnosis of intestinal leiomyositis was made after evaluation by a pathologist (PP). Dog 4 underwent a gastroduodenoscopy and biopsy procedure 5 days before exploratory laparotomy, and a diagnosis of mild lymphoplasmacytic enteritis of the stomach and duodenum was made on mucosal pinch biopsies.

All dogs underwent exploratory laparotomy, and none of them had evidence of mechanical obstruction at the time of surgery. Five of the 6 dogs had segmentally to diffusely dilated fluid-filled stomachs and small intestines, most notably the jejunum. The jejunum and ileum were markedly friable and edematous in dog 5. Dog 4 reportedly had a normal exploratory laparotomy. Full-thickness intestinal biopsies were obtained in all 6 dogs, and an enlarged mesenteric lymph node was removed from dog 6 for histopathology and aerobic bacterial culture. Culture in thio broth yielded scant growth of *Escherichia coli*, *Bacteroides uniformis*, and

Bacteroides thetaiotaomicron, all being susceptible to most antimicrobials tested.

Histopathologic Findings

Full-thickness sections of jejunum (6/6), stomach (5/6), ileum (4/6), colon (4/6), and esophagus (4/6) were reviewed. In all 4 dogs (dogs 1, 2, 3, and 6) in which necropsy was performed, previous biopsies were available for review with the interval between biopsy and necropsy being between 5 days (dog 4) and 10 months (dog 5). In 2/4 dogs (dogs 2 and 5) from which pancreata were available for review, a regional acute necrotizing pancreatitis was identified. This finding was interpreted to be secondary to the proximity of the pancreas to the intestine, because the region of the duodenum adjacent to the affected pancreas was highly inflamed and compromised. Smooth muscle within esophagus, spleen, systemic vasculature, gall bladder, urinary bladder, and lung were examined and was histologically unremarkable except in 1 case. In dog 1, the smooth muscle of the third eyelid had inflammation similar in character to that seen in the intestine. Histopathology of the stomach and intestines identified mild to marked mononuclear infiltration, myofiber degeneration, and fibroplasia or fibrosis centered within the muscularis externa of the intestinal walls. The jejunum was the most severely and chronically affected segment of the bowel in all dogs (Fig 2A,B), and most dogs had concurrent inflammation of the duodenum and ileum. The colon and stomach were available for review in 4/6 and 5/6 dogs, respectively, and lesions were present, but milder than those seen in the small intestine (Fig 3). Skeletal muscle was within normal limits in all 6 dogs.

In early lesions (as judged by quantity, distribution, and balance of inflammation and fibrosis), inflammation and degeneration were segmental, random within either the circularis or longitudinal layers and spared the

muscularis mucosae (Fig 2). In the most severe, and presumably most chronic lesions, segments of the muscular wall were entirely replaced with fibrosis or fibroplasia (Fig 4A). A histochemical trichrome stain (Fig 4B) and immunohistochemistry (IHC) for smooth muscle actin or desmin^a (Fig 4C) identified marked smooth muscle loss with replacement by fibrous tissue. In some segments of the jejunum, the submucosa and adventitia were nearly in direct apposition (Fig 4A–C). The intensity of inflammatory cells infiltrating these regions varied widely. By IHC analyses, infiltrative cells were primarily T lymphocytes (CD3 positive^b, Fig 5A, B), with regionally similar or less intense infiltration of B cells (CD20^c and CD79^c positive, Fig 5C), and lesser numbers of histiocytes (CD18^d positive). The most severely affected segment in 1 dog was edematous and contained perivascular neutrophils. In severely affected segments, the smooth muscle fibers were widely separated or obscured by the inflammation (Figs 2, 3, 5). Immunohistochemistry stains for neuron-specific enolase^e and GFAP^f highlighted the location of the enteric plexuses, which although not specifically targeted by the inflammation, were at times surrounded by the inflammation in segments that were severely and transmurally affected. Evaluation of all sections indicated that the plexuses within the submucosa or between the muscle layers were not involved in the inflammatory process. Special stains for bacteria (modified Gram's stain), fungus Grocott's methenamine silver stain (GMS), periodic acid–Schiff stain (PAS), and other organisms (Giemsa, Warthin Starry, Acid-fast) were negative in all dogs.

Clinical Outcome

Information on long-term outcome was available in all 6 dogs. All dogs received multidrug treatment consisting of various combinations of immunomodulatory treatment, prokinetic treatment, antimicrobial agents, antiemetics, and IV fluids. Dogs 1 and 2 developed

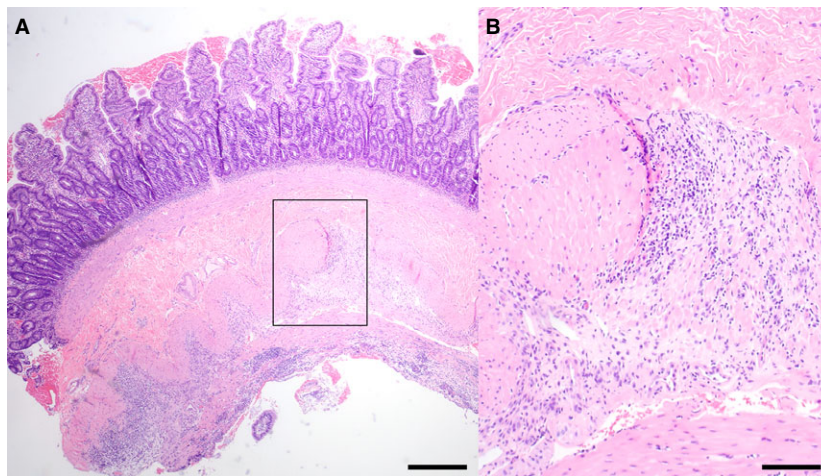


Fig 2. Jejunum. Severe, lymphocytic leiomyositis from dog 3. (A) The circular and longitudinal muscles contain dense infiltrates of inflammatory cells. The muscularis mucosae and mucosa are within normal limits. Bar = 800 μ m. (B) Boxed inset. In this segment of the muscular wall there is muscular loss with replacement by a combination of fibroplasia and inflammation. Bar = 150 μ m. Hematoxylin and eosin.

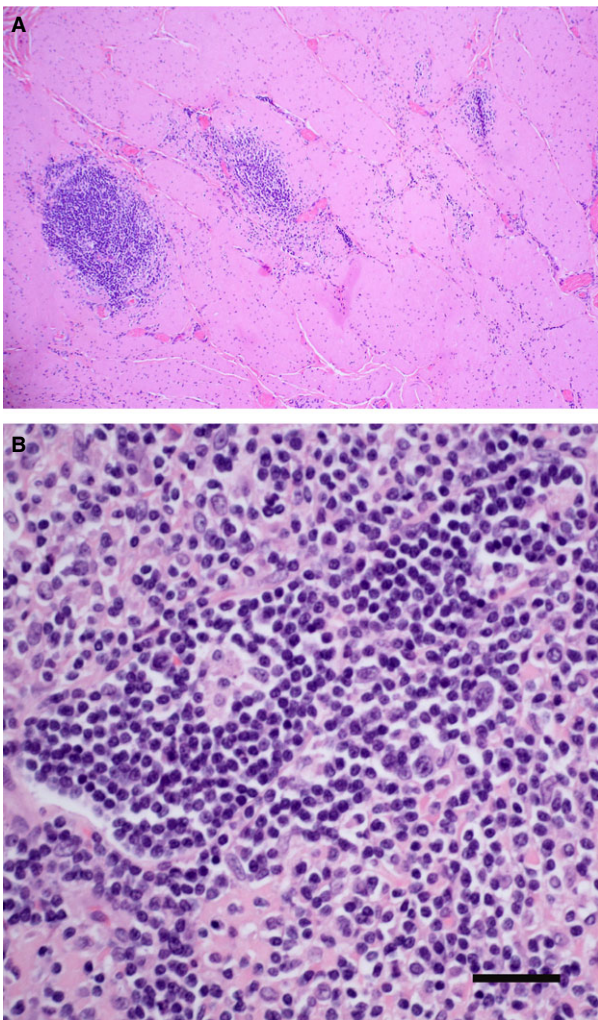


Fig 3. Stomach. Mild, multifocal leiomyositis from dog 2. Fig 3A (Lower magnification): Scattered aggregates of lymphocytes within and obscuring segments within the muscular wall. Fig 3B (higher power magnification): The inflammation is predominantly lymphocytes, with fewer scattered plasma cells and macrophages (Bar = 50 μ m). Hematoxylin and eosin.

progressive aspiration pneumonia and despite aggressive medical treatment were euthanized at days 20 and 18 after diagnosis, respectively, because of declining quality of life. Dog 3 was discharged from the hospital on PO medications including prednisone (1.5 mg/kg PO q12 h), cyclosporine^l (5 mg/kg PO q12 h), cisapride (0.5 mg/kg PO q8 h), metronidazole^j (13 mg/kg PO q12 h), and cyanocobalamin (1,000 μ g SC q30d). After 9 months of treatment, the dog represented for inappetence, and humane euthanasia was elected because of declining quality of life. Dog 4 was discharged on prednisone (1 mg/kg PO q12 h), erythromycin^k (1 mg/kg PO q8 h), omeprazole^l (0.9 mg/kg PO q24 h), maropitant^m (1 mg/kg PO q24 h), metoclopramideⁿ (0.22 mg/kg PO q8 h), amoxicillin (20 mg/kg PO q12 h), metronidazole^j (20 mg/kg PO q12 h), azithromycin^o (10 mg/kg PO q24 h), and Hill's Prescription

Diet i/d[®] dog food.^p Approximately 14 days after discharge, the dog was euthanized because of lack of response to treatment. Dog 5 was hospitalized and treated postoperatively with hetastarch^q (1 mg/kg IV constant rate infusion [CRI]), metoclopramideⁿ (2.2 mg/kg/day IV CRI), sucralfate^r (1 g PO q8 h), maropitant^m (1 mg/kg IV q24 h), and CliniCare[®] liquid diet^s via nasogastric tube. Despite continued medical treatment, the dog continued to deteriorate and humane euthanasia was elected within 3 days of admission. Dog 6 was discharged without medical treatment before histopathologic diagnosis, and was evaluated at a follow-up visit 12 days postoperatively. At reevaluation, the dog had a ravenous appetite and had gained 0.5 kg with improved, but unresolved small bowel diarrhea and 1 episode of vomiting. A repeated abdominal ultrasound examination showed persistently dilated small intestine loops and midabdominal lymphadenomegaly. Medical management was initiated with prednisone (0.5 mg/kg PO q12 h), cyclosporine^l (5 mg/kg PO q12 h), cisapride (0.5 mg/kg PO q12 h), and Hill's Prescription Diet i/d[®] low fat dog food.^t Three weeks later, the dog was reevaluated and was clinically stable. Additional treatment with cyanocobalamin (800 μ g SC q7d for 6 weeks, and monthly thereafter) and a commercially available probiotic (VSL#3^u at 225 billion CFU/day) was implemented. Initially, the dog responded clinically to treatment, but it deteriorated after 10 weeks and humane euthanasia was elected. Overall, the median survival among the affected dogs was 19 days after diagnosis (range, 3–270 days).

Discussion

This report describes the largest case series of dogs with chronic intestinal pseudo-obstruction attributed to intestinal leiomyositis, with several unique features in the dogs' clinical presentation, involvement of extraintestinal tissues, and outcome. Most dogs with this condition are evaluated for assessment of chronic vomiting, regurgitation, diarrhea, anorexia, and weight loss,^{2–8} but 5/6 dogs in this series displayed abnormal clinical signs for ≤ 2 weeks and only 1 of 6 dogs (dog 3) had evidence of weight loss during its evaluation. This dog had a history of chronic vomiting and diarrhea, likely contributing to its weight loss, whereas clinical signs in all of the other dogs were acute in nature.

Clinicopathologic changes were variable and non-specific in all 6 dogs. Radiographic and ultrasonographic imaging of the abdomen disclosed variable involvement of the stomach, small intestine, and colon in all dogs, with diffuse dilatation of the small intestine in all 6 dogs, dilatation of the stomach and small intestine in 5 dogs, and dilatation of the small and large intestine in 2 dogs. The loss of gastric and jejunal wall layering noted on 2 dogs by ultrasonography likely was associated with obliteration of the muscularis layer, resulting in near apposition of the submucosa and adventitia in severe cases (Fig 3A–C).

In 6/6 dogs that underwent exploratory celiotomy and in most of the previously reported cases,

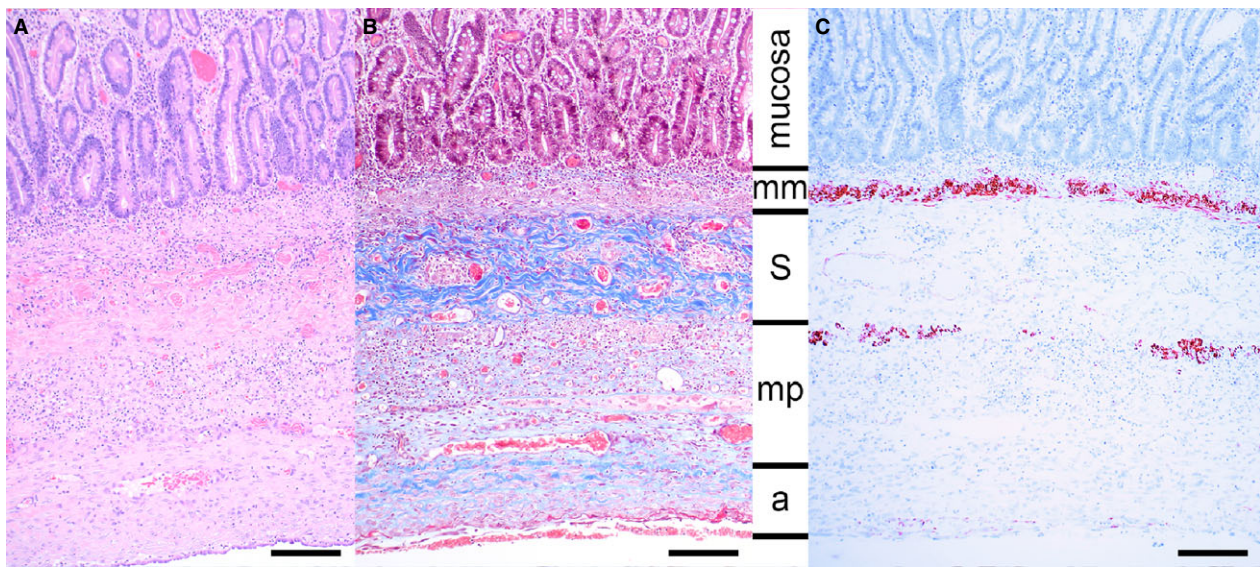


Fig 4. Jejunum. Severe segmental leiomyositis, replicate serial sections from dog 2. (A) The submucosa is in nearly direct apposition with the adventitia, with scattered lymphocytes present throughout the remnant muscular wall. Hematoxylin and eosin. Bar = 200 μ m. (B) Blue-stained collagen completely replaces the muscularis propria (mp). Trichrome stain. (C) An antibody-recognizing desmin reveals the extent of the muscular loss, with only remnant short segments in the innermost segment of the muscularis propria, and in this severe case mild disruption of the muscularis mucosae (mm). Immunohistochemistry, antidesmin.

mechanical obstruction secondary to foreign body was an important diagnostic consideration.^{8,14,16} Dog 1 had an abdominal CT scan performed at the VMTH 11 days postoperatively because mechanical obstruction was suspected, and abdominal ultrasound examination at the VMTH was consistent with intraluminal foreign material. The CT scan allowed visualization of the luminal contents of all dilated bowel loops without obstructive material, further refuting the presence of mechanical obstruction. Despite the added cost and anesthetic risk, the CT scan prevented a second exploratory laparotomy being performed on the dog. We recommend abdominal CT as an adjunctive imaging modality, particularly in large breed dogs with gas-distended intestinal loops, in which abdominal ultrasonography has important limitations. We advocate survey radiographs of the abdomen in all dogs in which mechanical obstruction is suspected, and the procedure was highly informative in 3 of the 4 dogs in which it was performed. Abdominal ultrasound examination was performed in 5 dogs and was highly informative in all of them. The primary differential diagnosis in all dogs in this case series was mechanical versus functional GI obstruction. We found that combining complementary imaging modalities such as abdominal radiographs with ultrasonography was the most effective method to rule out the presence of a mechanical obstruction, although all dogs ultimately went to surgery for exploratory celiotomies to confirm this suspicion.

As in dog 1, obtaining multiple full-thickness gastric and intestinal biopsies is essential to make a definitive diagnosis in cases having a negative exploratory laparotomy.^{1,17,18} Surgical intervention presents potential risks of exacerbating ileus as a consequence of anesthetic protocols, intraoperative manipulations, and potentially

the formation of postoperative adhesions. However, because the inflammatory infiltrate primarily affects the muscularis propria layer, and the mucosa is spared (Fig 2), partial-thickness endoscopic biopsies are inadequate to establish a diagnosis as noted in dog 4 in which initial endoscopic biopsies were nonspecific and did not identify evidence of leiomyositis. Because of the lack of full-thickness intestinal biopsies in many dogs with chronic enteropathies and the overall lack of awareness of this condition among veterinarians, we suspect this condition is underdiagnosed in dogs undergoing endoscopic evaluation alone. In addition, the initial histopathologic diagnosis from dog 1's full-thickness GI biopsies was severe lymphocytic-plasmacytic gastritis and enteritis, but after further review by pathologists at UC Davis, a diagnosis of intestinal leiomyositis was made. An overall lack of awareness and recognition of this disorder likely led to the initial misdiagnosis of the dog's enteropathy. Laparoscopy-assisted GI biopsy is commonly practiced in human patients and the procedure minimizes *de novo* adhesion formation, but has no efficacy in decreasing adhesion formation after adhesiolysis.¹⁹ Antroduodenal manometry is an adjunctive procedure that may help differentiate mechanical from functional forms of intestinal occlusion, and was found useful in human patients with CIPO and gastroparesis.²⁰

In our study, either necropsy material or full-thickness intestinal biopsies were diagnostic. The consistent histologic findings were T-lymphocyte inflammation within the muscularis propria, with relative sparing of the mucosa, submucosa, and neural plexuses. Myofibers appear to be the targets of the inflammation, because they are present in various stages of degeneration and necrosis, with the most striking finding being nearly

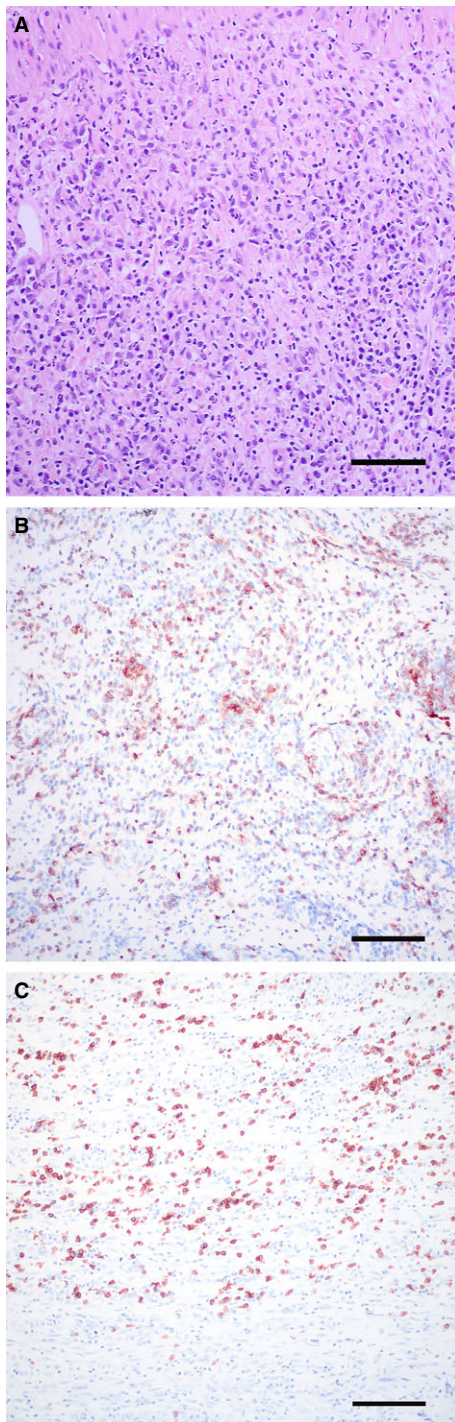


Fig 5. Jejunum, muscularis propria from dog 1. (A) Severe, diffuse leiomyositis (Hematoxylin and eosin). (B) Immunohistochemistry using an antibody recognizing the CD3 portion of the T-cell receptor reveals that the majority of infiltrative cells are T cells. (C) Immunohistochemistry within the same section as (B), using an antibody that recognizes the B-lymphocyte antigen CD20. Bar = 100 μ m.

complete myofiber loss in chronic disease (Fig 4). Nonetheless, because the mechanism for this condition remains unclear, these cases could represent more than

1 pathogenesis. In human patients, the inflammatory reaction is specific for the intestinal musculature, because smooth muscle fibers of vessels within the intestine and smooth muscle in other tissues are unaffected. Humans with intestinal leiomyositis can have autoimmune disease as a preexisting condition.¹⁸ None of the dogs in our case series had concurrent evidence of autoimmune disease based on results of laboratory testing and histopathology of multiple tissues, including endocrine organs, lymph nodes, spleen, and bone marrow, but further testing for autoimmune disease was not pursued utilizing tests to detect antinuclear neuronal antibodies (ANNA-1) as has been shown to be of value in human patients with lymphocytic myenteric ganglionitis.²¹

No breed predispositions have been identified to date, but all dogs in our series were large breeds. Two of the dogs in this series were Portuguese Water dogs and one of the dogs was a Bernese Mountain Dog, a breed previously reported to have intestinal leiomyositis.² Other canine breeds diagnosed with leiomyositis and reported in the literature include the Yorkshire Terrier, Border Collie, American Staffordshire Terrier, English Bulldog, Kerry Blue Terrier, English Springer Spaniel, German Shepherd Dog, and mixed breed dogs.³⁻⁸ Previously reported ages of affected dogs have ranged from 6 months to 10 years old.⁷ In this case series, the ages of the affected dogs ranged from 15 months to 9 years, highlighting the importance of considering this disorder both in younger and older animals. In addition, dog 6 was from Finland and the onset of its GI signs occurred while in Finland, indicating that this disorder has a wide geographic distribution.

Leiomyositis affecting extragastrointestinal organs is becoming an increasingly reported entity in humans and dogs, and clinical signs may reflect organs affected. In our case series, dog 1 initially presented with protrusion of the nictitating membrane, and histopathology confirmed leiomyositis of the third eyelid. A previous publication described a dog afflicted with intestinal and urinary bladder leiomyositis that also presented with protrusion of the nictitating membrane, similar to dog 1.⁶ In that study, however, histopathology was not performed to confirm involvement of the nictitating membrane.

Management of intestinal leiomyositis in humans is supportive generally and aimed at relieving signs arising from intestinal dysmotility as well as optimizing nutritional support.^{1,17} Prokinetic treatment is a mainstay of treatment, and cisapride has been shown to increase the antroduodenal motility index and improve enteral feeding in people as well as to increase lower esophageal sphincter (LES) pressure and decrease gastroesophageal reflux in dogs.²²⁻²⁴ Metoclopramide is a less potent and effective prokinetic agent compared to cisapride in dogs.²⁵ Other agents such as subtherapeutic doses of erythromycin, azithromycin, or erythromycin-derived motilin agonists have been shown to stimulate antral motility in humans and dogs with functional or experimentally induced gastric obstructions.^{26,27}

Immunosuppressive agents including corticosteroids, cyclosporine, cyclophosphamide, and azathioprine have been utilized in humans with documented intestinal leiomyositis or when the disease is suspected based on the presence of circulating antibodies, with most success occurring early in the disease process.¹ Progression of disease leads to intestinal fibrosis, often resulting in refractoriness to immunomodulatory treatment. Additionally, bacterial dysbiosis and impaired intestinal motility are closely associated, and can contribute to increased intestinal inflammation, bloating, and translocation, further impairing motility.²⁸ There is no common agreement concerning choice, dosing, and duration of antibiotic treatment in humans with small intestinal bacterial overgrowth (SIBO). In general, long-term treatment with broad-spectrum antibiotics is suboptimal because such a treatment can be associated with dysbiosis, diarrhea, *Clostridium difficile* expansion, and possibly increase resistance to antibiotics. A multi-strain probiotic containing *Lactobacillus casei*, *Lactobacillus plantarum*, *Streptococcus faecalis*, and *Bifidobacterium brevis* also was shown to be more effective than metronidazole for resolving clinical signs in human patients with SIBO and functional chronic abdominal distension.²⁹ Serum cobalamin concentrations should be monitored and cobalamin supplemented if warranted in dogs with ileus, given the association with bacterial dysbiosis. In our case series, serum cobalamin concentrations were measured only in 2/6 dogs, but ideally should have been measured in all animals.

Maximizing enteral feedings has been shown to markedly improve GI health in humans with CIPO,^{1,17} although parenteral nutrition coupled with minimal enteral feedings may provide added benefits in preventing regurgitation and aspiration pneumonia, as seen in dog 2. Two dogs received commercially available canned diets^{p,t} and showed initial clinical improvement. Recommendations for dietary management of humans with CIPO include the utilization of low-fiber and fat-restricted liquid formulas, and gastrostomy or jejunostomy feeding tubes are commonly utilized to ensure adequate caloric intake.³⁰ In patients with severe gastroparesis, a low-profile gastrostomy device can be placed to periodically vent air from the stomach.³⁰ Additional studies are warranted to determine the optimal nutritional treatment for dogs with intestinal leiomyositis and the role of utilizing limited antigen diets or protein hydrolysates. In human patients with severe CIPO refractory to medical treatment, near total small bowel resection can be an effective treatment to relieve clinical signs and improve health and quality of life, although such patients remain dependent on home parenteral nutrition.³¹ No dogs in our case series underwent an enterectomy at any stage of their management.

Unfortunately, despite continuous medical advances, the prognosis for people and dogs with CIPO secondary to intestinal leiomyositis is poor, with mortality rates up to 35% documented in people.³² All dogs were euthanized as a consequence of their intestinal disease in our series, with a maximum survival time of 9 months in dog 3. Histologically, dog 3 had mild to moderate

intestinal leiomyositis at the time of diagnosis, whereas the other dogs in the study had more severe intestinal pathology (including fibrosis) at initial diagnosis. We speculate that dog 3 was diagnosed earlier in its disease process and that the cyclosporine treatment given at the time of diagnosis might have delayed further progression of the disease process before irreversible fibrosis of the muscularis propria occurred.

Primary causes of death in humans are related to complications associated with parenteral nutrition administration, surgical complications, or septic shock of GI origin.¹ Although GI resections are utilized in patients with segmental disease, this approach is not recommended routinely and is considered a salvage procedure because surgery can precipitate clinical deterioration, and any benefits achieved often are temporary, because of the progressive nature of the disease. Unfortunately, the dogs in our case series ultimately were euthanized because of their intestinal dysmotility or aspiration pneumonia. The outcome and prognosis for this disorder likely will not improve without earlier diagnosis, although this is challenging in dogs that likely have subclinical disease for weeks to months before diagnosis. Additional research is warranted to better understand the pathogenesis of this disorder, particularly in those breeds in which it has previously been reported.

Footnotes

- ^a Desmin and Smooth muscle actin, BioGenex, Fremont, CA
^b CD3 (T cell), Peter Moore, UCD SVM, Davis, CA
^c CD20 (B cell), Neomarker, Waltham, MA
^d CD18 (histiocyte), Peter Moore, UCD SVM, Davis, CA
^e CD79 (B cell), AbD Serotec, Kidlington, UK
^f IDEXX Laboratories, Inc., Westbrook, ME
^g Neuron specific enolase, Invitrogen, Grand Island, NY
^h Glial fibrillary acidic protein, DAKO, Carpinteria, CA
ⁱ Atopica, Novartis Animal Health US, Inc., Greensboro, NC
^j Flagyl, Pfizer, New York, NY
^k E.E.S (erythromycin ethylsuccinate), Abbott Laboratories, Abbott Park, IL
^l Prilosec, Procter and Gamble, Inc., Cincinnati, OH
^m Cerenia, Zoetis, Florham Park, NJ
ⁿ Reglan, Teva Pharmaceuticals, Sellersville, PA
^o Zithromax, Pfizer, New York, NY
^p Hill's Prescription Diet i/d[®] canned, Hill's, Topeka, KS
^q Hextend, Hospira, Inc., Lake Forest, IL
^r Carafate, Teva Pharmaceuticals, Sellersville, PA
^s CliniCare[®] liquid diet, Abbott Animal Health, Abbott Park, IL
^t Hill's Prescription Diet i/d[®] low fat canned, Hill's, Topeka, KS
^u VSL #3, Sigma-Tau Pharmaceuticals, Inc., Gaithersburg, MD
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