ORIGINAL ARTICLE

Endoscopic and surgical treatment of non-neoplastic proximal duodenal ulceration in dogs, and anatomical study of proximal duodenal vascularisation

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Objectives: Proximal duodenal ulceration is often characterised by continuous bleeding, and treatment is challenging. The aims of this study were to investigate the role of vascularisation in proximal duodenal ulceration and describe clinical aspects, endoscopic features and treatment in dogs.

Material and Methods: Polyurethane foam casts of gastroduodenal vessels were obtained from five dogs which had died from disorders unrelated to the digestive system. In addition, 12 dogs having proximal duodenal ulcers diagnosed by endoscopic examination were enrolled in a treatment trial. After the endoscopic diagnosis of a duodenal ulcer, all the dogs were treated medically and, in the absence of resolution, were subsequently treated by endoscopic electrocauterisation or by surgery.

Results: A submucosal vascular network was evident in all the casts, with a prominent venous plexus seen exclusively in the first half inch of the duodenum. In clinical cases, on endoscopic examination, the duodenal ulcer was located at the proximal part of the duodenum, involving the mesenteric portion of the wall. The dogs not responding to medical treatment (6/12) were treated with endoscopic electrocauterisation, surgical coagulation or resection of the proximal duodenal portion. All the dogs survived until discharge, and the median survival time following discharge was 107.5 days.

Clinical Significance: Based on the anatomical details highlighted in this study, the continuous bleeding observed in our patients may have been due to the prominent venous plexus evidenced at the level of the proximal duodenum. Surgical and endoscopic treatments in six patients resolved the ulcer bleeding with no recurrences noted during follow-up.

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INTRODUCTION

A peptic ulcer is a mucosal defect in which the entire epithelial thickness, down to or through the basement membrane, has been lost (Zachary, 2021). The lesion can be found in the stomach or in the duodenum, called a gastric or a duodenal ulcer, respectively. In contrast to erosions, which affect only the surface epithelium with a minimal inflammatory response, an ulcer can extend into the *muscularis mucosae* (Sullivan & Yool, 1998).

The development of peptic ulceration appears to be multifactorial, resulting from the exposure of the mucosal barrier to proteolytic enzymes, toxins, reactive oxygen species, microbes and drugs. This leads to the development of inflammatory, erosive and, ultimately, ulcerative lesions, by altering the physiological defences of the mucosa through a disruption of the muco-bicarbonate barrier, increased gastric secretion of hydrochloric acid and a reduced mucosal blood flow (Liptak *et al.*, 2002; Marks *et al.*, 2018; Park *et al.*, 2023).

Macroscopically, the gross appearance of an ulcer varies according to its aetiology, severity and duration, from a flat lesion to a round or oval parietal defect, with a smooth base and perpendicular borders (Amorim *et al.*, 2016). Chronic ulcers usually differ from acute ulcers by the presence of an indurated rim caused by fibrosis and attempts at epithelial regeneration (Zachary, 2021).

The risk factors, clinical signs and comorbidities of gastroduodenal ulcers have been investigated in veterinary medicine (Cariou *et al.*, 2009; Jergens *et al.*, 1992), and although clinical signs and predisposing causes may overlap between gastric and duodenal ulcers, the severity of the clinical manifestation, the persistence of clinical signs and the treatment may differ between the two forms.

Although duodenal ulcers are less common than gastric ulcers, it has been reported in human medicine that bleeding and subsequent perforation are more frequent in duodenal ulcers (Stanton & Bright, 1989; Wang *et al.*, 2020). Severe gastrointestinal bleeding can give rise to severe anaemia which complicates patient management (Wang *et al.*, 2020). Many gastric or duodenal ulcers are refractory to medical management, necessitating the development of additional surgical or interventional therapies in veterinary patients. Endoscopic treatment is known in human medicine to provide important clinical benefits in patients with active bleeding (Laine *et al.*, 2021). In contrast, the use of endoscopic electrocautery for a duodenal ulcer as an alternative to surgery has never been reported in spontaneously affected dogs.

Furthermore, in human medicine, attempts are being made to clarify the role of duodenal microvascularisation in the development of duodenal peptic ulcers; however, these attempts remain incomplete in veterinary medicine (Murakami *et al.*, 1999; Wilhelm *et al.*, 2020).

Given the scarcity of literature specifically related to duodenal ulcers in dogs, the aims of this observational study were: (1) to investigate the distribution of vessels in the proximal duodenum and assess whether vascular anatomy is contributing to the persistent ulceration at this site, and (2) to describe the clinical features, endoscopic findings and interventional therapy of dogs with duodenal ulcers refractory to medical management.

The hypothesis was that vascularisation at the site of a proximal duodenal ulcer could explain severe, medically refractory bleeding.

The PubMed and Scopus databases were searched using the following keywords "dog and duodenal ulcer and endoscopic treatment" on February 1, 2023. Only one paper related to the comparison of the efficacy and histologic injury of bipolar electrocoagulation and argon laser photocoagulation in the treatment of experimentally induced (and not spontaneous) oesophageal and duodenal ulcers in dogs was found (Machicado *et al.*, 1981). No reports of endoscopic treatment of spontaneous canine duodenal ulcers were found when carrying out these searches.

MATERIALS AND METHODS

The study was divided into two main phases.

The first phase was a *post-mortem* study to investigate the vascularisation of the proximal duodenum in dogs without gastrointestinal diseases, while the second phase was focused on the clinical, endoscopic and therapeutic description of canine duodenal ulcers occurring spontaneously. The second phase dogs were referral patients diagnosed by endoscopic examination that, upon failing medical therapy, then underwent surgical or endoscopic electrocautery.

The study was carried out according to the Italian legislation which implemented the European Council Directive 2010/2063 regarding the protection of animals used for scientific purposes; informed consent was obtained from all dog owners before the beginning of the study.

Phase 1

Polyurethane foam casts of duodenal vascularisation

To investigate the role of vascularisation in ulcer persistence, polyurethane foam casts of the gastroduodenal vessels were obtained from 5 dogs differing in sex, age, weight and breed which had died owing to causes unrelated to the gastrointestinal or cardiovascular systems.

The technique of creating polyurethane foam casts of the gastroduodenal vessels followed the method proposed by De Sordi *et al.* (2014). Briefly, the portal vein and, after opening the thoracic cavity, the first tract of the descending aorta were catheterised and washed with tap water to remove blood and clots. For the arterial system, an extension tube, shortened (approx. 50 cm) and cut to make the tip pointed, was inserted into the thoracic aorta and a haemostatic clamp was positioned to close the abdominal aorta after the origin of the coeliac artery.

For the portal system, the portal vein was used and catheterised by a similar catheter. The casts of these vessels were obtained by injecting 40 g of polyurethane foam (diphenylmethane-4, 4-diisocyanate; Soudafoam – Soudal N.V., Turnhout, Belgium), diluted with 10 mL of pure acetone into each bloodstream in order to prevent its expansion, and then adding a few drops of red, or blue nitro dye (PebeoCeramic, Gemenos Cedex, France), for the arterial and the venous systems, respectively.

The abdomen was then covered with soaked absorbent paper to ensure the correct anatomical position and to avoid dehydration, and each dog was cooled to 4°C for 5 hours to allow the foam to set.

The stomach and the duodenum were then isolated, cut at the mesenteric edge and gently rinsed using a water jet. Finally, a morphological study was carried out; the images were acquired using a reflex digital camera (Fujifilm HS50) and were processed using Adobe Photoshop CS7®.

Phase 2

Subject selection

In this observational case series study, the records from November 2016 to January 2022 were searched for dogs which were presented to the Veterinary Hospital, and were diagnosed with proximal duodenal ulcers. The inclusion criteria for case selection were dogs of any age, breed and sex which had clinical signs related to acute or chronic ulcers which had undergone an endoscopic examination of the digestive tract and had been diagnosed with a duodenal peptic ulcer. Dogs with gastric ulcers, with duodenal neoplastic ulcers and with ulcers associated with the concomitant presence of gastrointestinal foreign bodies were excluded. Dogs with duodenal ulcers and other comorbidities were also enrolled.

All cases enrolled in the study had undergone a diagnostic investigation (complete history, clinical presentation, clinicopathological evaluation and ultrasound examination findings) to exclude other causes of gastrointestinal bleeding before undergoing endoscopic examination.

The following data were recorded for the dogs: signalment; history with particular attention to the presence of previous episodes of vomiting, haematemesis, diarrhoea or melaena, and any possibly recent treatment with non-steroidal anti-inflammatory drugs (NSAIDs), or corticosteroids; clinical presentation; laboratory findings, such as blood count, biochemistry, coagulation panel and abdominal ultrasound findings, to look for increased duodenal wall thickness, periduodenal oedema, hyperechoic periduodenal fat and enlargement of pancreaticoduodenal and hepatic lymph nodes.

In addition, for each dog enrolled, the gastrointestinal endoscopic diagnosis, including the aspects of the duodenal mucosa, and the treatment (medical, endoscopic or surgical) of the ulcers were reported.

Duodenal ulcer diagnosis

All the endoscopic examinations were performed by the same expert endoscopist (MP) in a standardised fashion based on the American College of Veterinary Internal Medicine (ACVIM) Consensus Statement (Washabau *et al.*, 2010), using the same endoscope (Pentax EG-2970, diameter 9.8 mm).

Anaesthetic protocol was based upon the patients-specific American Society of Anesthesiologists (ASA) criteria and decided at the anaesthetists discretion.

The dogs were placed in left lateral recumbency to facilitate the transpyloric passage of the endoscope; the endoscopic procedure was performed using duodenal dilatation with lukewarm water (Galiazzo *et al.*, 2020). The pattern of the mucosal surface, the shag carpet appearance created by the villi, the major (and occasionally the minor) duodenal papilla and the Peyer's patches were examined.

All the procedures were recorded using a software package (Pinnacle Studio 22 Plus, Corel Corp., Ottawa ON, Canada) and, after the gastroenteric endoscopic procedure, the descriptive characteristics of the lesions were assessed.

The following aspects were recorded for each case: (1) the affected side of the proximal duodenum (dorsal, ventral, medial-mesenteric side, lateral-antimesenteric side); (2) the presence of a single lesion or multiple ulcerating lesions and (3) the width of the ulcer. To describe the width of the lesion, the size was expressed in degrees: 90° for lesions occupying one quadrant, 180° for those occupying two quadrants, 270° for those occupying three quadrants, and 360° if it extended for the entire circumference of the duodenal surface (Fig 1). The macroscopic description was obtained by evaluating four main characteristics: (1) number of lesions recorded; (2) description of the ulcer crater (flat ulcer versus slightly excavated ulcer versus deep ulcer; (3) ulcer wall thickening (thickened versus non-thickened); (4) description of the margins (hyperaemic versus non-hyperaemic)

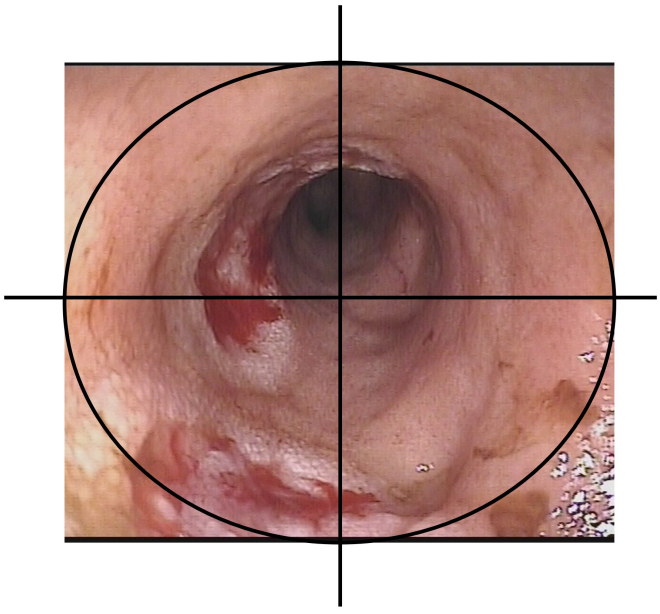

FIG 1. Evaluation of the width of the ulcer. Size was expressed in degrees: 90° for lesions occupying one quadrant, 180° for lesions occupying two quadrants, 270° for lesions occupying three quadrants and 360° if it extended around the entire circumference of the duodenal surface

and (5) presence of bleeding from the ulcer (bleeding versus no bleeding).

At the time of the endoscopy, three to five biopsies were taken from the ulcer site (crater and wall) and from normal-appearing tissue and immediately placed in formalin. Biopsies were analysed by the board-certified pathologist to confirm the nature of the ulcer (benign or malignant).

Type of treatment

After the endoscopic diagnosis of a duodenal ulcer, all the dogs were started on medical treatment (omeprazole 1 mg/kg SC twice daily, sucralfate 40 mg/kg PO three times daily, and amoxicillin and clavulanate 12.5 mg/kg SC twice daily). In the absence of clinical/laboratory resolution within approximately 10 days (based on the disappearance of vomiting, haematemesis, melaena and/or loss of haematocrit point), the lesions were subsequently treated by endoscopic electrocauterisation or by surgery.

The ulcer showing active bleeding on endoscopic examination, in the absence of major areas of necrosis, underwent electrocoagulation (Alsa Apparecchi Medicali SRL, Castelmaggiore, Italy) using a monopolar endoscopic electric snare (Endoaccess Gmbh, Garbsen, Germany). A monopolar technique is applied with a strong thermal effect capable of producing coagulation and haemostasis in the intestinal wall, with the result of clot formation in the submucosal vessels.

Surgery was performed if the duodenal wall involved extensive areas of necrosis, with or without active bleeding, or if the characteristics of the ulcer (position, duodenal diameter) prevented endoscopic treatment. Surgery included direct coagulation using bipolar electrosurgical forceps *via* duodenotomy or, in the case of diffuse necrosis, *via* duodenectomy and subsequent gastroduodenal anastomosis (Billroth type 1).

Statistical analysis

All the data were analysed using a statistical software package (MedCalc Statistical Software version 19.5.1, Ostend, Belgium). All the continuous variables were tested for their distribution using the Shapiro–Wilk normality test. Descriptive statistics included mean ±sd for normally distributed data, and median and range (minimum to maximum) for data that were not normally distributed.

RESULTS

Phase 1

Polyurethane foam cast

Observation of the vascular structure revealed that the blood supply to the C-shaped duodenum was shared with the head of the pancreas. The proximal segment of the duodenum was supplied by the gastroduodenal artery and its branches, including the cranial pancreaticoduodenal artery. Venous drainage follows the arteries and ultimately drains into the portal system.

In all the specimens, a submucosal vascular network, both venous and arterial, was evident, with a prominent venous plexus seen in detail exclusively in the first half inch of the duodenum (Fig 2).

Phase 2

Signalment

Thirty-seven cases were assessed, and 12 cases met the inclusion criteria. Four subjects were excluded due to a lack of historical and diagnostic data, while another nine were excluded due the simultaneous presence of a gastrointestinal foreign body, and

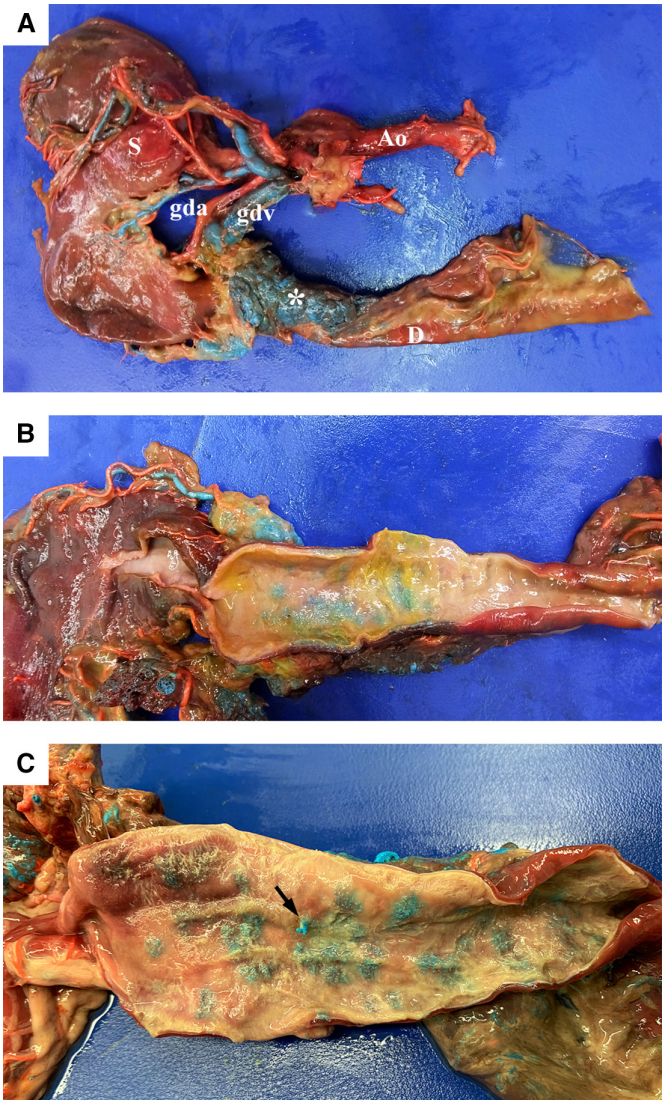

FIG 2. Polyurethane foam cast (sample after foam curing and isolation). (A) Ventral view of the dog's stomach (S) and duodenum (D). The gastroduodenal artery (gda) and vein (gdv) are clearly visible, as is the aorta (Ao). The venus plexus is on the mesenteric border of the first duodenal tract (*). (B) The duodenum was sectioned at the antimesenteric border, at the level of the venous plexus, to better view the mucosal vascularisation. Note the vein vascularisation in blue. (C) A detail of the mucosa. Note the presence of a venous vessel (arrow) protruding from the surface of the mucosa

12 for a concomitant gastric ulcer. The breeds included four mixed breed dogs, two German shepherd dogs and one of each of the following breeds: Flat-coated retriever, Italian short-haired hound, Bernese mountain dog, American Staffordshire terrier, Pinscher and Labrador retriever. Sex and neuter status included five males (three neutered) and seven females (five spayed). A mean age of 7 ±4 years and a mean bodyweight of 24 ±13 kg were reported (Table 1).

History and clinical presentation

At the time of hospitalisation, the most common historical and presenting clinical signs were lethargy (9/12), dysorexia (10/12), vomiting (8/12), melaena (8/12), pale mucous membranes (7/12) and haematemesis (2/12); abdominal pain (1/12) was less frequently reported (Table 2).

All dogs had comorbidities, namely chronic enteritis, chronic pancreatitis, exocrine pancreatic insufficiency, chronic kidney disease, immune-mediated thrombocytopenia and pulmonary carcinoma. In one dog, a predisposing factor was previous treatment with lomustine, and then with masitinib mesylate, for cutaneous lymphoma, ending 1 month before endoscopy, and, in a second dog, treatment, a few days before, with a drug containing a non-steroidal anti-inflammatory (diclofenac diethylammonium). The ASA physical status classification was recorded before the anaesthesia in all patients (Table 2).

Common clinicopathological findings (8/12 dogs) were severe normochromic (MCHC 31.05 ±1.7%) normocytic (MCV 70.31 ±7.46 FI) regenerative (208,012 ±192,763 RET/mm^3) anaemia (HCT 17.6 ±6.6%). All eight cases with severe anaemia had severe hypoproteinaemia (4.62 ±0.71 g/dL) and hypoalbuminaemia (2.1 ±0.99 g/dL) (Table 3).

Abdominal ultrasound, performed on 11 of 12 cases, showed increased duodenal wall thickness (6/11), periduodenal oedema (1/11) and hyperechoic periduodenal fat (4/11) (Table 4).

Due to severe anaemia, a blood transfusion was required in seven of 12 dogs before the endoscopy.

Table 1. Signalment and bodyweight of the dogs with proximal duodenal ulceration

	Breed	Sex	Age	Weight (kg)
Case 1	Pinscher	F	2y 1m	5.7
Case 2	Mixed breed	S	6y 7m	13
Case 3	Mixed breed	N	13y 11m	11.7
Case 4	German shepherd dog	M	10y 5m	36.6
Case 5	Italian short-haired hound	F	1y	11
Case 6	Mixed breed	M	13y 2m	27.5
Case7	German shepherd dog	S	6y 8m	42
Case 8	American Staffordshire terrier	S	1y 6m	17.9
Case 9	Flat-coated retriever	N	9y 7m	30
Case 10	Bernese mountain dog	N	3y 11m	47
Case 11	Labrador retriever	S	4y 5m	25.2
Case 12	Mixed breed	S	5y 6m	21.5

Gender: M Male, N Neutered male, F Female, S Spayed female; Age: y Year, m Month

Endoscopic visualisation and histological diagnosis

The duodenal ulcers were located at the proximal part of the duodenum before the duodenal papillae (major and, eventually if present, minor). In all cases, they involved the mesenteric portion of the wall, extending to the dorsal portion in two of 12 cases, to the dorsal and ventral portions in one case, and having an incomplete ring appearance in two of 12 cases (Fig 3A), also involving, the dorsal side, the ventral side and part of the lateral side, in addition to the medial wall. The surface area of the proximal duodenum involved ranged from 90° to 360°. In nine of 12 cases, the lesion was single, while in two cases, there were two lesions in close proximity, and in the remaining case, there were multiple lesions. On endoscopic examination, the ulcers appeared flat in five of 12 dogs (Fig 3B), slightly excavated in five of 12 dogs and deep in two of 12 dogs; in seven of 12 dogs, they were associated with wall thickening (Fig 3C) and in seven of 12 with hyperemic margins. Active bleeding was recorded during endoscopy in 10 of 12 patients.

The full findings, treatment procedures and histological diagnosis are summarised in Table 5.

Treatments and outcome

Medical treatment was started after the first endoscopy diagnosing the ulcer. All the dogs received proton-pump inhibitors,

Table 2. Historical and presenting clinical signs of the dogs with proximal duodenal ulceration

	Predisposing factors/co-morbidities	Lethargy	Dysorexia	Vomiting	Hematemesis	Melaena	Pale mucous membranes	Abdominal pain	ASA score
Case 1	Immune-mediated thrombocytopenia	Yes	Yes	Yes	No	Yes	Yes	No	3
Case 2	Previous treatment with masitinib mesylate and lomustine for cutaneous lymphoma	Yes	No	No	No	Yes	Yes	No	3
Case 3	Chronic kidney disease	Yes	Yes	Yes	Yes	Yes	Yes	No	3
Case 4	Exocrine pancreatic insufficiency	Yes	Yes	No	No	Yes	Yes	Yes	3
Case 5	Immune-mediated thrombocytopenia	Yes	Yes	Yes	Yes	Yes	Yes	No	3
Case 6	Chronic enteritis	Yes	Yes	No	No	No	Yes	No	3
Case 7	Chronic enteritis, chronic pancreatitis	No	Yes	No	No	Yes	Yes	No	3
Case 8	/	Yes	Yes	Yes	No	Yes	No	No	3
Case 9	Pulmonary carcinoma	Yes	Yes	Yes	No	Yes	No	No	3
Case 10	Chronic enteritis	No	No	Yes	No	No	No	No	2
Case 11	Chronic enteritis	Yes	Yes	Yes	No	No	No	No	2
Case 12	NSAIDs ingestion (Diclofenac)	No	Yes	Yes	No	No	No	No	2
Total	11/12	9/12	10/12	8/12	2/12	8/12	7/12	1/12	12/12

NSAIDs Non-steroidal anti-inflammatory drugs, ASA American Society of Anesthesiologists – Physical Status Classification System

Table 3. Clinicopathological variables in dogs with proximal duodenal ulceration

	HCT % RI 32 to 48	MCHC % RI 31 to 38	MCV Fl RI 60 to 77	RET/ mm³ RI 0 to 60,000	PLTs/ mm³ RI 200,000 to 400,000	TP g/dL RI 5.74 to 7.65	Alb g/dL RI 2.7 to 3.9	PT sec RI 6.5 to 8.9	aPTT sec RI 8 to 16.5
Case 1	10.8	28.3	83.7	419,000	18,000	3.58	1.77	7.2	13.7
Case 2	23.2	30.9	63.7	62,600	114,000	4.89	2.14	7.2	14.4
Case 3	13.7	30.9	76.3	133,300	596,000	5.8	2.99	5.1	10.5
Case 4	13.8	33.2	61.2	562,000	562,000	3.94	1.25	8.4	14.5
Case 5	10	28.7	66.2	267,900	239,000	4.64	2.29	6	11.6
Case 6	18.8	31.8	74.9	89,500	401,000	5.16	2.23	7.4	14.2
Case7	21.3	32.3	67.2	114,700	784,000	4.83	2.14	5.3	8.5
Case 8	29	32.3	69.3	15,100	293,000	4.15	2.01	6.4	11.7
Case 9	38.9	34.4	68.6	39,900	420,000	6.65	3.1	7	11.2
Case 10	44.1	33.1	70.2	143,900	369,000	6.03	2.64	6.2	8.2
Case 11	44.3	34.1	64.4	194,800	624,000	6.66	3.42	5.2	9.3
Case 12	51.6	34.1	72	278,700	273,000	4.8	2.05	7.4	12.4
Mean	26.6	32.0	69.8	193,450	391,083	5.1	2.3	6.6	11.7
SD	14.6	2.0	6.2	163,791	222,367	1.0	0.6	1.0	2.3

HCT Haematocrit, MCHC Mean corpuscular haemoglobin concentration, MCV Mean corpuscular volume, RET Reticulocyte, PLTs Platelets, TP Total protein, ALB Albumin, PT Prothrombin time, aPTT Activated partial thromboplastin time, RI Reference interval

Table 4. Ultrasonographic evaluation of the duodenum and the lymph nodes in close proximity

	Increased duodenal wall thickness	Peri-duodenal oedema	Hyperechoic peri-duodenal fat	Enlargement of the pancreaticoduodenal lymph nodes	Enlargement of the hepatic lymph nodes
Case 1	No	No	No	No	No
Case 2	No	No	No	No	No
Case 3	Yes	No	No	No	No
Case 4	Yes	Yes	Yes	No	No
Case 5	Yes	No	Yes	No	No
Case 6	Yes	No	No	No	No
Case7	No	No	No	No	No
Case 8	Yes	No	No	No	No
Case 9	Yes	No	Yes	No	No
Case 10	ND	ND	ND	ND	ND
Case 11	No	No	Yes	No	No
Case 12	No	No	No	No	No
Total	6/11	1/11	4/11	0/11	0/11

ND Not determined

sucralfate and antibiotics. The dogs which did not respond to medical treatment in 10 days (6/12) were subsequently treated with endoscopic electrocauterisation (Fig 4) (4/6), surgical coagulation *via* duodenotomy (1/6), or complete resection (enterectomy) of the proximal duodenal portion, and a gastroduodenal anastomosis (Billroth type 1) (1/6). Surgical and endoscopic treatments successfully resolved the ulcer bleeding, without any recurrences, regardless of the predisposing factors. All the dogs survived to discharge. The median survival time [excluding cases lost to follow-up (case 4 and case 10)] was 107.5 days (10 to 1946) (Table 5). Of the four dogs that died, case 2 died 471 days after the diagnosis of gastric ulcer due to a recurrence of cutaneous lymphoma. Case 7 died 10 days after discharge from acute pancreatitis. Case 9 died after 206 days from lung cancer. Case 11 died after 17 days from septic peritonitis; the owners declined an autopsy.

DISCUSSION

The clinical findings associated with gastroduodenal ulcers in dogs have already been extensively described in veterinary medicine (Cariou *et al.*, 2009; Daure *et al.*, 2017; Dobberstein *et al.*, 2022; Duerr *et al.*, 2004; Hinton *et al.*, 2002; O'Kell *et al.*, 2022; Pavlova *et al.*, 2021; Stanton & Bright, 1989). However, with few exceptions (Saravanan *et al.*, 2012), there was a lack of knowledge regarding the description of the ulcers located in the duodenum and on their therapeutical treatment, whether medical, surgical, or as a new approach, endoscopic electrocautery.

In order to better understand the reason for the localisation of ulcers in the proximal duodenal, an anatomical study of the vascularisation of this part of the intestine was included. The vessels injected with the foam were thoroughly filled, confirming what has previously been described in horses and other species (Grandis *et al.*, 2021; Martín-Orti *et al.*, 2022; Ramadania *et al.*, 2022). The authors found an evident submucosal vascular network in the first half inch of the duodenum, proximal to the duodenal papillae in all the specimens examined. The prominent venous plexus, seen in detail in the foam casts, could explain the location of the bleeding in this part of the canine duodenum, and it should be emphasised that the anatomical features of the proximal duodenal venous network described herein represented an element which had not previously been reported in dogs. It is

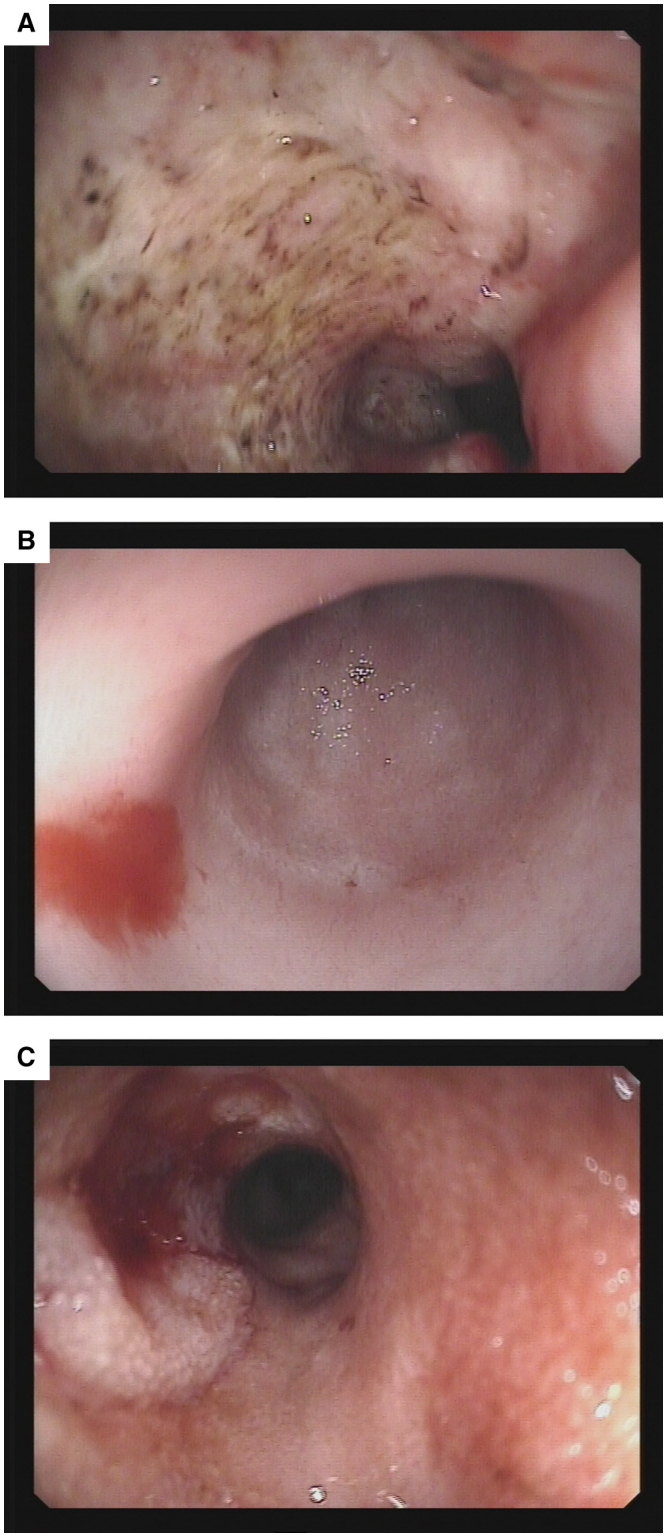

FIG 3. Endoscopic findings of proximal duodenal ulcers. (A) Wide ulcer extension with an incomplete ring appearance. (B) A flat proximal duodenal ulcer. (C) Proximal duodenal ulcer with wall thickening

worth noting that the apparent vascularization of the proximal duodenum does not concur to be a main justification for the development of the ulcer, it could otherwise explain its persistence over time and its tendency not to heal spontaneously.

Due to the small population enrolled in the study, conclusions cannot be drawn regarding the breeds most at risk, although predominantly medium/large breeds were identified, such as those which have already been reported in previous studies (Cariou *et al.*, 2009; Hinton *et al.*, 2002). A greater predisposition to intestinal ulcer perforation in German Shepherds has already been reported in the literature (Poortinga & Hungerford, 1998). In the present study, two German Shepherds were included; the first (case 4) was lost to follow-up, and the second (case 7) did not respond to medical therapy, and was euthanased 10 days after the endoscopic procedure. For gastroduodenal ulcerative disease of non-neoplastic origin, the mean age reported in a previous study was 6 years (from 5 months to 14 years) (Stanton & Bright, 1989) which is consistent with the mean age of the canine population in the present study (7 years – from 1 to 13 years). In fact, although duodenal ulcers can occur in animals of any age, predisposing factors are more common in adult-older animals.

The clinical signs most commonly reported in the population in this study include lethargy, dysorexia, vomiting, melaena and pale mucous membranes, which are clinical signs similar to those already reported in the literature for gastroduodenal ulcers (Fitzgerald *et al.*, 2017; Hinton *et al.*, 2002; Stanton & Bright, 1989). Anaemia was a common finding, affecting 67% of the dogs enrolled, predominantly with normochromic normocytic characteristics. In several dogs (7/12), haemorrhage from gastrointestinal bleeding was severe enough to require blood transfusions. Hypoalbuminaemia was present in 75% of the dogs and was often associated with a decrease in total protein. In addition, acute or chronic anaemia and hypoproteinaemia are common findings in gastrointestinal ulcers (Cariou *et al.*, 2009; Fitzgerald *et al.*, 2017; Saravanan *et al.*, 2012; Stanton & Bright, 1989). External blood loss causes loss of plasma protein and erythrocytes; therefore, hypoproteinaemia (with a proportional decrease in albumin and globulin) combined with regenerative anaemia strongly suggests substantial ongoing or recent external blood loss (Harvey, 2012). Other laboratory findings were non-specific and reflected changes associated with vomiting, blood loss and inflammation.

Several diseases and predisposing factors have been suggested to promote the development of gastroduodenal ulcers in dogs, including neoplasia, renal disease, gastrointestinal disease, hepatobiliary disease, administration of NSAIDs or corticosteroids, and elevated stress (Dobberstein *et al.*, 2022; Jergens *et al.*, 1992; Pavlova *et al.*, 2021; Reed, 2022). The population in the present study had heterogeneous comorbidities; the limited number of patients examined did not allow the authors to statistically investigate their role. Furthermore, several vascular abnormalities which could be associated with gastrointestinal bleeding have been reported in humans (varices, haemorrhoids, vascular ectasia, angiodysplasias and Dieulafoy's lesions) (Xie *et al.*, 2022), while, in dogs, only one case of Dieulafoy's lesion has recently been described, characterised by dilated, large-calibre, aberrant submucosal arteries eroding the epithelium, and causing massive and potentially fatal haemorrhage into the gastric lumen (Murillo *et al.*, 2022). The limited number of cases presented herein may justify the absence of hepatobiliary diseases as being among the causes of the ulceration; hepatobiliary diseases are

Table 5. Descriptive characteristics for a detailed description of the duodenal ulcers

	Ulcer location (side)	Ulcer width (degree)	N of lesions	Crater	Walled	Margins	Bleeding	Ulcer treatment	Histological diagnosis	Alive/ outcome
Case 1	M	120°	1	Flat ulcer	Not thickened	Not hyperemic	Yes	Endoscopic cauterization	Moderate enteritis – LP infiltrate	365 days/ Alive
Case2	M	90°	1	Flat ulcer	Thickened	Not hyperemic	Yes	Endoscopic cauterization	Moderate enteritis – LPE infiltrate	471 days/ Euth NR
Case3	M	120°	1	Flat ulcer	Not thickened	Hyperemic	Yes	Endoscopic cauterization	Moderate enteritis – LP infiltrate	64 days/ Alive
Case4	M	90°	1	Deep ulcer	Thickened	Hyperemic	No	Medical treatment	Severe enteritis with pseudomembranes	9 days/LTF
Case 5	M	150°	1	Flat ulcer	Not thickened	Not hyperemic	Yes	Surgical cauterization	Severe subacute enteritis with mild fibrosis	1946 days/ Alive
Case 6	M	90°	1	Slightly excavated ulcer	Not thickened	Not hypermic	Yes	Endoscopic cauterization	Severe chronic enteritis	80 days/ Alive
Case7	M/D/ V/L	300°	>2	Flat ulcer	Thickened	Hyperemic	Yes	Medical treatment	Severe enteritis – LPE infiltrate	21 days/ Euth UR
Case 8	M/D/ V/L	240°	1	Deep ulcer	Thickened	Hyperemic	Yes	Medical treatment	Moderate enteritis – LPE infiltrate	135 days/ Alive
Case 9	M/D/V	300°	1	Slightly excavated ulcer	Thickened	Hyperemic	No	Enterectomy	Severe chronic enteritis with fibrosis	206 days/ Euth NR
Case 10	M/D	180°	2	Slightly excavated ulcer	Not thickened	Hyperemic	Yes	Medical treatment	Severe acute enteritis	14 days/ LTF
Case11	M/D	180°	2	Slightly excavated ulcer	Thickened	Not hyperemic	Yes	Medical treatment	Severe enteritis – LPE infiltrate	17 days/ Euth NR
Case 12	M	210°	1	Slightly excavated ulcer	Thickened	Hyperemic	Yes	Medical treatment	Severe chronic enteritis	34 days/ Alive

Ulcer localization: M Medial portion of the duodenal bulb, D Dorsal portion of the duodenal bulb, V Ventral portion of the duodenal bulb, L Lateral portion of the duodenal bulb, L Lymphocytes, P Plasma cells, E Eosinophils, Euth Euthanased, NR Non-related to ulcer disease, UR Ulcer related, LTF Lost to follow-up

often reported as being predisposing factors in the literature (Pavlova *et al.*, 2021).

In the present study population, abdominal ultrasound findings regarding duodenal ulcers were not consistently reliable, with a 55% incidence of non-specific increased duodenal wall thickness in the affected patients. The latter was not entirely surprising, as several studies have reported a low sensitivity of abdominal ultrasound examination for the detection of non-perforated gastroduodenal ulcers in dogs (Fitzgerald *et al.*, 2017; O'Kell *et al.*, 2022; Weston *et al.*, 2022). Conversely, as previously reported by Saravanan *et al.* (2012), the endoscopic approach seemed to be the most accurate technique for the early diagnosis of duodenal mucosal ulcers, useful both in defining the extent of the lesion, and for selecting the appropriate treatment.

The different aspects of the ulcers which can be identified in the endoscopic examination are probably linked to the severity or duration of the process, as the less severe ulcers had a flat surface, whereas the more severe ones were characterised by more or less deep depressions with thickened edges. Furthermore, although the limited number of dogs enrolled in the study must be taken into account, the aspect of the ulcer did not appear to influence the outcome, as only one of 12 patients affected by a flat ulcer, was euthanased for ulcer-related reasons. Similar to what has been reported in human medicine in which duodenal peptic ulcers were the major cause of upper gastrointestinal bleeding events (Mönig *et al.*, 2002), in the present study, active bleeding was also frequently observed during the endoscopic procedures (10/12 patients), regardless of possible anaesthetic-induced reduction in blood pressure, which could hide the bleeding. However, hypotensive phases were not recorded in this study. In humans, severe bleeding from duodenal peptic ulcers has been attributed to the peculiar extraluminal course of the gastroduodenal arteries (Wilhelm *et al.*, 2020). The latter would favour the development of chronic bleeding, whereas, in dogs, as the present study showed, the same phenomenon seemed to be favoured by the presence of a rich venous network at the level of the proximal duodenum.

Following the literature (Lanas & Chan, 2017; Marks *et al.*, 2018), all the patients enrolled were treated with proton-pump inhibitors, sucralfate and antibiotics for 10 days after the first endoscopic procedure; however, half of them did not respond to medical treatment. The decision to subject patients with gastrointestinal ulcers to antibiotic therapy has been directly extrapolated from human medicine. Currently, antibiotic treatment for dogs with gastrointestinal ulcers is not recommended in veterinary medicine. The decision to wait approximately 10 days to repeat the endoscopic examination and to have the dogs undergo endoscopic or surgical therapy was guided by the clinical signs and clinical pathology findings of the dogs with ulcers. In fact, it is thought that a continuous loss of haematocrit points in the face of transfusions, and the persistence of

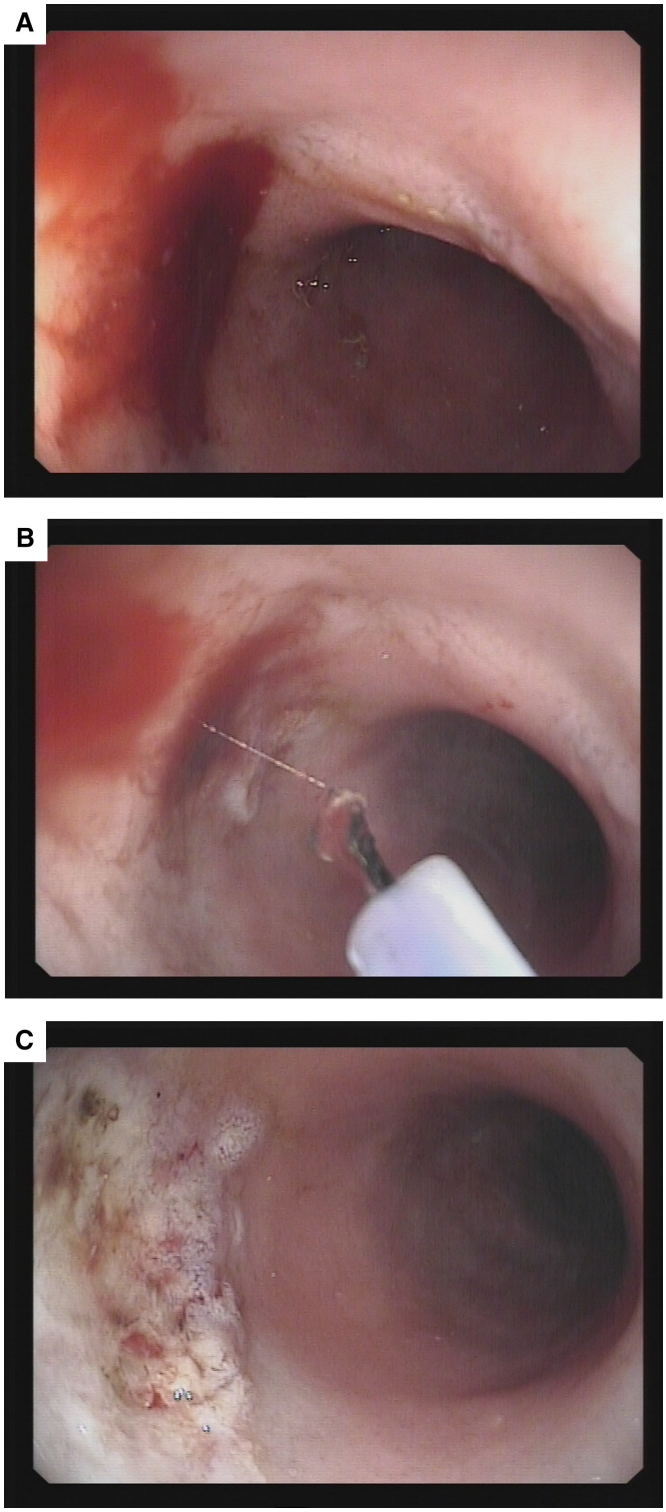

FIG 4. Endoscopic electrocautery resolution of a bleeding duodenal ulcer. (A) duodenal bleeding ulcer before resolution. (B) endoscopic electrocautery. (C) duodenal ulcer (clot formation) after endoscopic electrocautery

important clinical signs, such as vomiting and melaena, may be riskier for the dog than an interventional approach. Although the efficacy of proton-pump inhibitors in reducing rebleeding has been recognised in bleeding gastric ulcers, their efficacy in bleeding proximal duodenal ulcers may be somewhat limited. Of the factors which could contribute to the maintenance of duodenal bleeding, duodenal pH may play a role. In fact, the pH tends to be neutral at this level, with a value which varies from 6.5 to 7.3 during the inter-prandial phase (Malbert & Ruckebusch, 1993). However, it should be emphasised that gastric acid overproduction which is not effectively buffered by duodenal alkaline reflux, could alter this physiological value. Studies are needed to fully investigate and understand whether the pH value and the pathophysiological processes occurring at this level may be a predisposing factor for the development and persistence of ulcers in the proximal duodenum.

The authors chose to use a transendoscopic electrocautery for those ulcers which were actively bleeding, but were without extensive necrosis at the time of the endoscopic visualisation. Conversely, a surgical approach was chosen when the ulcer showed notable necrosis (case 9), with a complete resection of the proximal duodenal portion, or when the characteristics of the ulcer location together with the size of the duodenum made an endoscopic approach impossible (case 5). In this case, surgery was essential to visualise the lesion which was then treated with electrocautery without carrying out an enterectomy. The use of endoscopic electrocautery for a spontaneous duodenal ulcer as an alternative to surgery has never been reported in a clinical study regarding dogs. In human medicine, endoscopic therapy using a contact thermal device is commonly performed in cases of bleeding ulcers as the heat produced causes the coagulation of the blood vessels *via* vessel constriction, activation of the coagulation cascade and tissue oedema and coagulation (Laine *et al.*, 2021; Troland & Stanley, 2018). Thermal therapy involves the use of several different probes (*i.e.* heater probes, bipolar electrocautery or laser) to successfully achieve haemostasis (Laine *et al.*, 2021; Laine & McQuaid, 2009). Furthermore, the evidence of clinical benefits for thermal endoscopic treatment in improving the outcome of additional bleeding and mortality is reported in the American College of Gastroenterology (ACG) guidelines (Laine *et al.*, 2021; Laine & McQuaid, 2009). The major complications described are the risk of perforation in relation to the characteristics and the depth of the ulcer, and depend on the experience of the endoscopist (Laine & McQuaid, 2009). None of the patients in the present study had complications related to the endoscopic electrocautery procedure, and even considering the limitations already reported regarding the small number of patients treated, it could be said that this technique provided an effective and minimally invasive procedure.

This study had some limitations which should be highlighted. Although all medical records are compiled in software which allows detailed retrieval of all patient information, the retrospective nature of the study may have resulted in minor approximations on the timing and treatments administered. Another limitation is related to the medical antibiotic treatment carried out in the patients in this study. Although the antibiotic administration in the dogs in the present study was carried out for prophylactic purposes and based on studies carried out on human medicine, there was no evidence that the use of antibiotics would be of benefit in the treatment of duo-

denal ulcers. Moreover, in the face of the current problem of antibiotic resistance, the use of antimicrobials for prophylactic purposes should be avoided. Due to the retrospective nature of the study, we did not have the opportunity to follow-up with each animal at standardised intervals. This limitation needs to be addressed in future studies.

In conclusion, anatomical studies have shown that the continuous bleeding which characterises these cases may be due to the prominent venous plexus at the level of the proximal duodenum which may inhibit ulcer healing. In cases where proximal duodenal ulceration in dogs do not respond to medical treatment, endoscopic electrocautery or surgical intervention could be considered viable treatment strategies.

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

Author contributions

Maria Chiara Sabetti: Conceptualization (equal); data curation (equal); writing – original draft (equal). **Veronica Cola:** Investigation (equal). **Armando Foglia:** Investigation (equal). **Dario Stanzani:** Data curation (equal). **Giorgia Galiazzo:** Data curation (equal); formal analysis (equal); investigation (equal); software (equal). **Simone Perfetti:** Investigation (equal). **Claudio Tagliavia:** Data curation (equal); investigation (equal); methodology (equal). **Luciano Pisoni:** Conceptualization (lead). **Marco Pietra:** Conceptualization (lead); writing – review and editing (equal).

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