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Case Report

Metastatic gastric adenocarcinoma associated with hypertrophic gastropathy resembling Ménétrier's disease in an adult Labrador Retriever dog

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Abstract

We describe a case of hypertrophic gastropathy (Ménétrier's like disease) with metastatic gastric adenocarcinoma in a seven-year-old intact female Labrador Retriever dog. The animal suddenly presented with emesis and died. Gross lesions included a marked diffuse thickening of the gastric mucosa and an ulcerated transmural neoplastic mass in the gastric body. Gastric body and fundus were affected by foveolar hyperplasia with loss of chief and parietal cells replaced by mucous cells and marked dilatation of gastric glands. An area of gastric adenocarcinoma with submucosal lymphatic vessels invasion was also present and metastases were observed in the gastric lymph nodes, small intestine, pancreas, lung and liver. Due to its similarity with other gastric proliferative disorders, including this condition in the list of differentials is a necessary step in the diagnostic investigation of canine gastropathies.

Key words: canine, stomach, hypertrophic gastropathy, adenocarcinoma, metastasis.

Introduction

Hypertrophic gastropathy is an acquired idiopathic gastric condition rarely reported in human beings (11). It is also known as giant hypertrophic gastropathy (10), hypoproteinaemic hypertrophic gastropathy or Ménétrier's disease (3). This lesion is macroscopically characterized by an extensive thickening of the gastric mucosa in a cerebriform pattern, accompanied by hypoproteinaemia (hypoalbuminaemia) and hypochlorhydria.

Microscopically, there is a diffuse hyperplasia of the foveolar epithelium with abundant mucin production and concurrent loss of oxyntic glands and gastric stroma (3, 7).

According to the human medicine literature, gastric carcinoma arises in about 6-10% of hypertrophic gastropathy human cases (6, 14, 17), and although the etiology of this pre-malignant condition is still unclear, there is a suspected association between its occurrence and different infections such as Cytomegalovirus, *Helicobacter pylori*, *Mycoplasma pneumoniae*, human immunodeficiency virus and herpes simplex virus (14).

In veterinary medicine, hypertrophic gastropathy is sporadically described in dogs (10, 12, 15, 16, 18, 19, 20), and one report in a cat (1) and in a camel (8). A few of these cases are reported in association with a gastric carcinoma (8, 10, 12). Here we describe a metastatic gastric adenocarcinoma associated with hypertrophic gastropathy in an adult Labrador Retriever dog.

Case report

A seven-year-old intact female Labrador Retriever dog was referred for recurrent dermatitis. The animal was regularly vaccinated and dewormed and had been previously diagnosed with demodicosis and dermatophytosis. Occasional emesis of unknown cause was previously observed. The dog was diagnosed with

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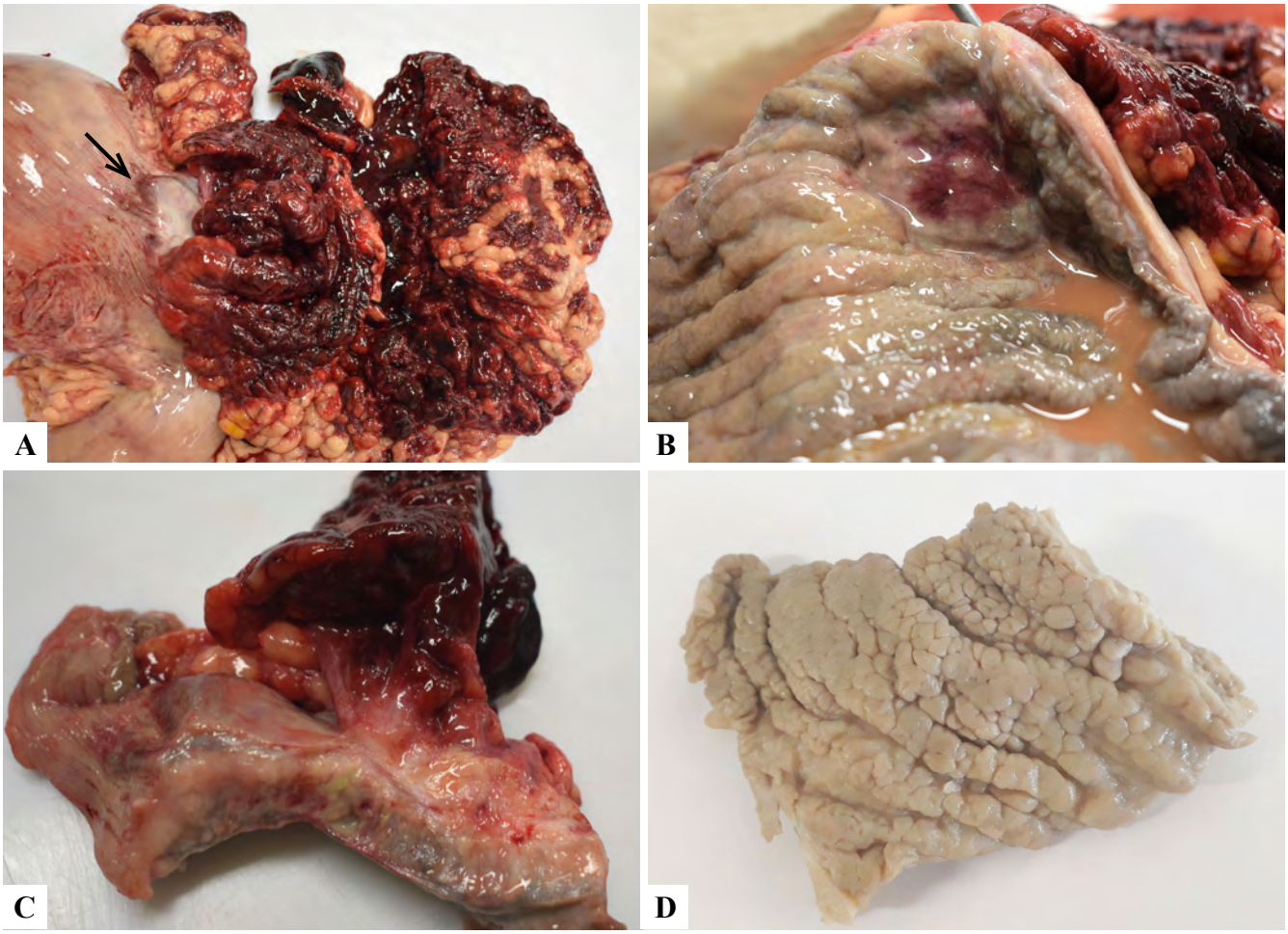

Figure 1. Gross findings in a dog with hypertrophic gastropathy and gastric adenocarcinoma. **A.** Omentum and stomach. Multifocal to coalescing areas of hemorrhage and multiple whitish and firm nodules adhered to omentum and gastric serosa (greater curvature and body of stomach) (arrow). **B.** Stomach. Focal ulceration associated with a tumor mass and diffusely thickened and edematous mucosa (body of stomach). **C.** Stomach. Transmural yellowish neoformation adhered to the omentum. **D.** Gastric mucosa diffusely thickened in a "cerebriform" pattern (fixed in 10% buffered formalin).

pyotraumatic dermatitis and received oral treatment with cefalexin (20 mg twice a day). After three days of treatment, the patient presented anorexia, vomit, and abdominal pain, and the treatment was interrupted. Since the clinical presentation was suggestive of gastritis, the patient was treated with oral ranitidine (2 mg/kg twice a day), aluminum hydroxide (20 mg/kg twice a day), simethicone (75 mg/kg three times a day), sucralfate (1 g/animal twice a day), and injectable metoclopramide hydrochloride (1 mg/kg three times a day). On the following day, the animal developed severe hematemesis and died on the eighth day after the onset of the treatment.

Postmortem examination revealed multiple whitish and firm, 1 mm to 2 cm nodules in the omentum, with multifocal acute hemorrhage and gastric serosa fibrous adhesions (Fig. 1A). In the gastric body greater curvature there was a whitish, 4.0 x 2.5 x 1.0 cm neoplastic mass, with yellow and friable areas arising from the focally ulcerated mucosa and extending to the serosa and greater omentum (Fig. 1B and 1C). The gastric body wall and the fundus regions were diffusely thickened up to 0.8 cm, and adjacent to an edematous and irregular mucosa forming a "cerebriform" pattern (Fig. 1D). Other significant gross findings included gastric lymphadenomegaly, with lymph nodes diffusely enlarged and reddish; 900 mL of clear peritoneal fluid (hydroperitoneum), and small and large intestinal distension with intraluminal serosanguineous fluid. The enteric mucosa was diffusely whitish and irregular. The right medial liver lobe contained a white and soft one cm nodule. The kidneys had multiple one mm in diameter well demarcated cortical areas of whitish discoloration. In the lungs, there was a moderate diffuse edema, with congestion and multifocal hemorrhage.

Samples of stomach, omentum, gastric lymph nodes, liver, lungs, small intestine, pancreas, kidneys, brain and uterus were collected for histopathological examination, fixed in 10% buffered formalin, paraffin-embedded, and 4 µm tissue sections on glass slides were stained with hematoxylin and eosin (HE), following a standardized histologic protocol. Stomach sections were also stained by periodic Schiff acid (PAS) and Warthin-starry techniques for mucous cells and for *Helicobacter pylori*, respectively.

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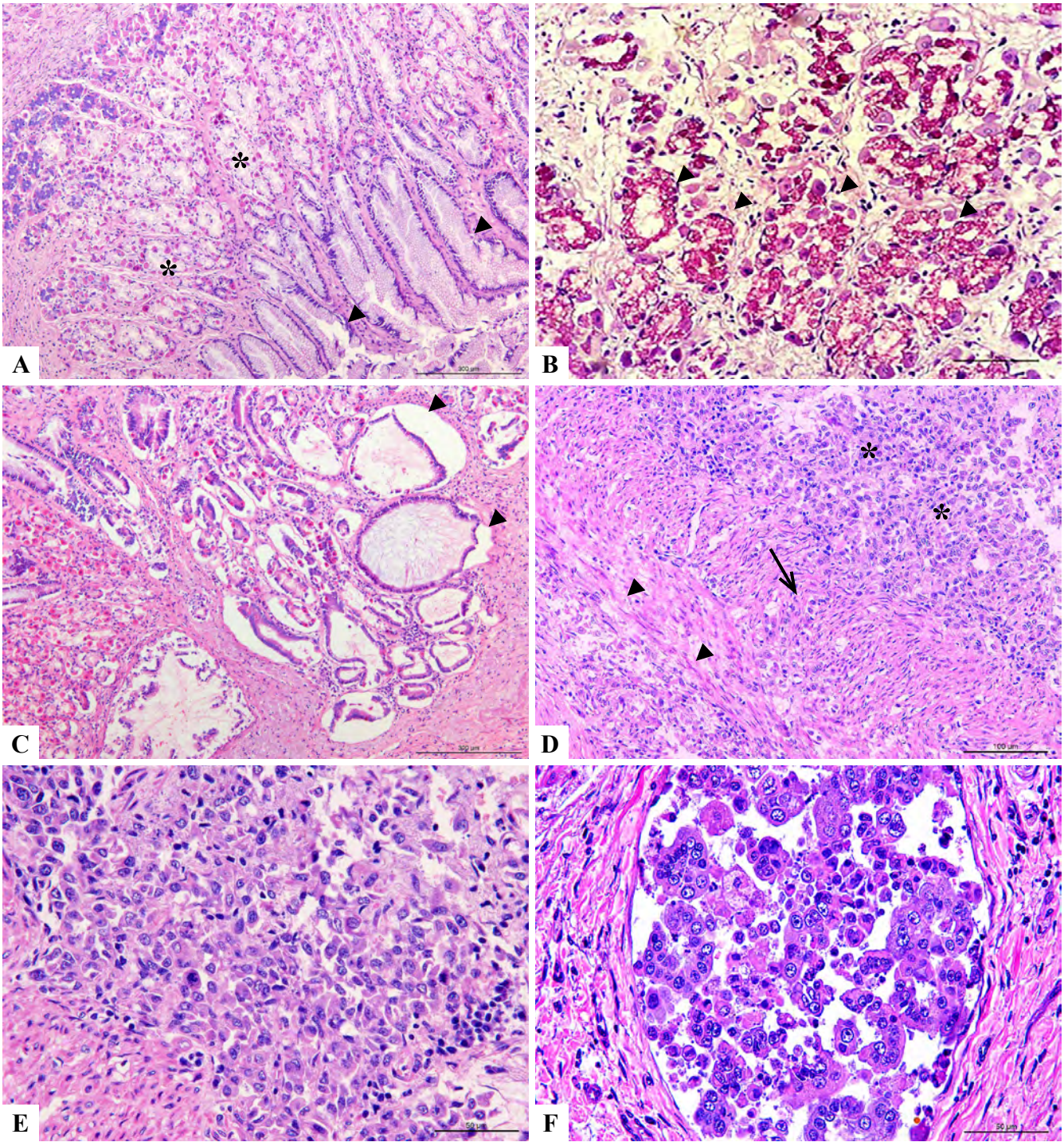

Figure 2. Histopathological findings in a dog with hypertrophic gastropathy and gastric adenocarcinoma. **A.** Gastric mucosa with foveolar hyperplasia (arrowheads) and replacement of oxyntic glands by mucous cells (asterisks) (HE). Obj. 10x. **B.** Detail of mucous cells in "A", stained in magenta (arrowheads) (PAS). Obj. 40x. **C.** Cystic dilation of gastric glands with intraluminal mucous accumulation (arrowheads), surrounded by fibrous tissue (HE). Obj. 10x. **D.** Gastric mucosa with malignant epithelial proliferation in a focally extensive ulcerated area (asterisks), overlying the invaded muscularis mucosa (arrow), and submucosal lymphatic vessels (arrowheads) (HE). Obj. 20x. **E.** Detail of neoplastic cells in "D" with a broad and eosinophilic cytoplasm, and a centrally located and round to oval nucleus with loose chromatin and prominent nucleoli, marked anisocytosis and anisokaryosis (HE). Obj. 40x. **F.** Submucosal lymphatic vessels filled with neoplastic cells individualized or arranged in acini (HE). Obj. 40x.

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Histologic lesions included marked mucosal thickening of the gastric body and fundic regions by foveolar hyperplasia forming irregular projections into the lumen (Fig. 2A). Replacement of oxyntic glands by mucous cells was particularly evident in the sections stained by PAS (Fig. 2B). Chief and parietal cells in the gastric glands were replaced by mucous cells and had intraluminal accumulation of amphophilic secretion (Fig. 2C). Warthin-starry argyrophilic histochemical stain of the stomach did not reveal any *Helicobacter pylori*. The gastric mass was neoplastic with cells disposed individually or in acinar arrangements (Fig. 2D). The cytoplasm was broad and eosinophilic, with centrally located nucleus that was round to oval with loose chromatin and prominent nucleoli. There was marked anisocytosis and anisokaryosis (Fig. 2E) with 15 mitoses in ten 40x magnification fields. Emperipolesis and a few multinucleated cells were also observed, and, in the submucosa, there was a moderate multifocal lymphoplasmacytic infiltrate. The gastric lymphatic vessels frequently contained neoplastic emboli with cytological features similar to the primary neoplastic site (Fig. 2F). The newly formed neoplastic acini were supported by a thick fibrovascular tissue stroma. The smooth muscle layers were diffusely thickened and disrupted by numerous neoplastic cells, occasionally reaching the omentum.

Metastatic emboli of the gastric adenocarcinoma were found within blood vessels and lymphatic sinuses of regional lymph nodes (Fig. 3A), small intestine mucosal and submucosal lymphatic vessels (Fig. 3B), blood vessels and interlobular septum of pancreas (Fig. 3C) and pulmonary vessels (Fig. 3D). Besides the metastatic lesions found in the lungs, there was also a marked edema, and several fibrinous thrombi within the arteriolar lumina. The hepatic nodule was histologically compatible with an area of metastasis. No other histologic lesions were found in the intestines to justify the hemorrhage. In the kidneys, there was chronic and moderate multifocal membranous glomerulonephropathy with mild glomerulosclerosis, intratubular hyalin casts and mild interstitial fibrosis.

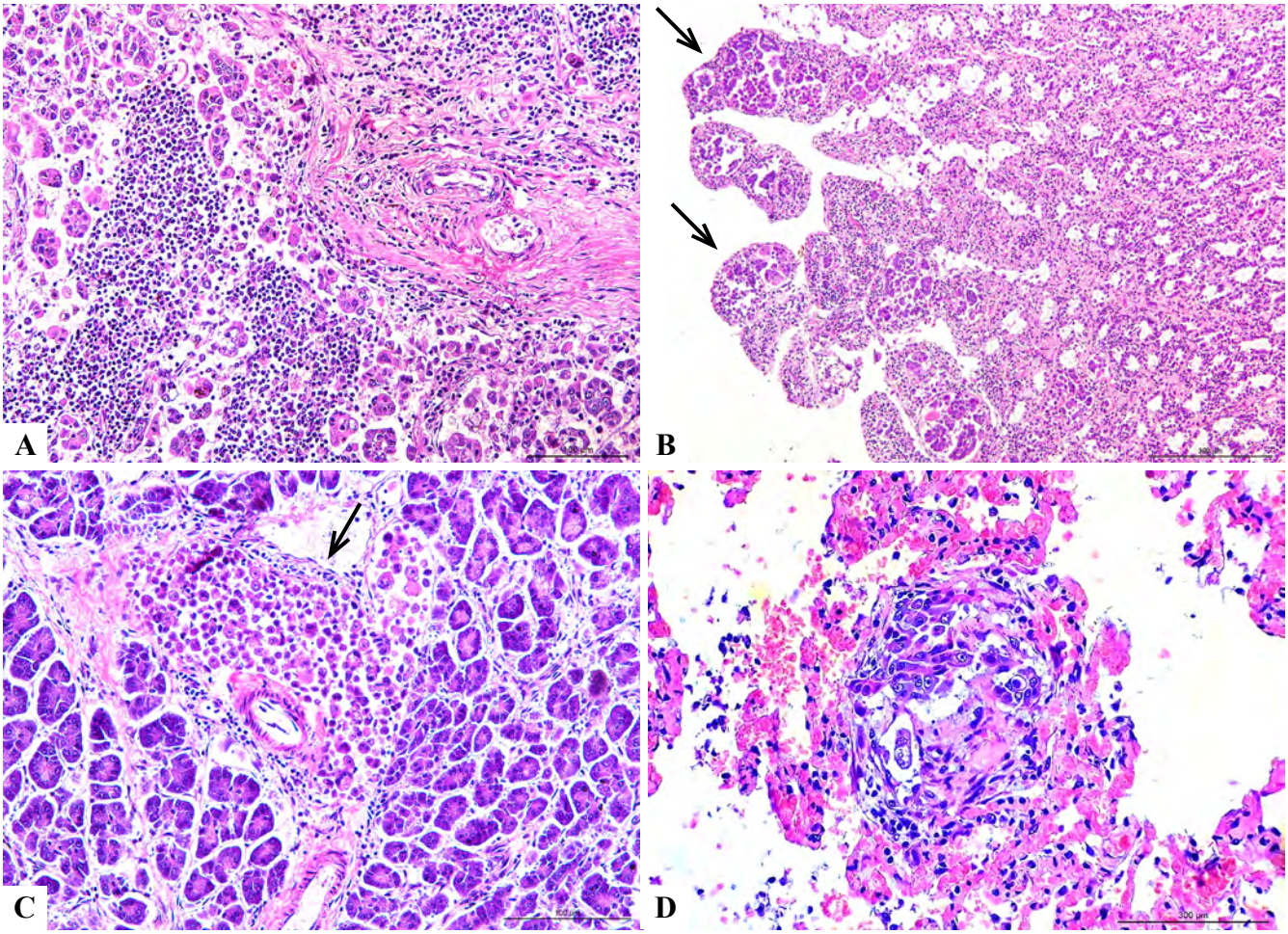

Figure 3. Microscopic findings of main metastatic sites from a dog with hypertrophic gastropathy and gastric adenocarcinoma. **A.** Gastric lymph node with numerous metastatic clusters into lymphatic sinuses (HE). Obj. 20x. **B.** Small intestine with emboli of the gastric adenocarcinoma within lymphatic vessels of the villi (arrows) (HE). Obj. 10x. **C.** Pancreatic interlobular septum with metastatic gastric adenocarcinoma (arrow) (HE). Obj. 20x. **D.** Lungs with metastatic emboli of the gastric adenocarcinoma within blood vessels (HE). Obj. 20x.

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Discussion

The anatomopathological findings in this dog are consistent with those found in hypertrophic gastropathy (Ménétrier's disease), associated with metastatic mixed-type gastric carcinoma. In humans, the condition may predispose to gastric adenocarcinoma (14), and occurrence of hypochlorhydria and hypoproteinemia (hypoalbuminemia) (3, 7), the last possibly justifying the hydroperitoneum and pulmonary edema observed in this dog.

Hypertrophic gastropathy has been described in different dog breeds, such as Boxer (18), Basenji (19), Old English Sheepdog (15), Cairn Terrier (12), West Highland White Terrier (10) and Jack Russell Terrier (20). This condition has also been described in a Labrador Retriever dog with hypertrophic gastropathy associated with gastric sarcoma (16). Here we describe hypertrophic gastropathy associated with gastric adenocarcinoma in a Labrador Retriever dog. Due to the scarcity of reports of this condition in dogs, especially of those with simultaneously association with gastric adenocarcinoma (10, 12), it is not certain whether the breed would play an important role in its occurrence. Previous reports of simultaneous conditions are restricted to dogs with Terrier genealogy (12).

Animals with hypertrophic gastropathy frequently present chronic and progressive anorexia, emesis, weight loss, hematemesis (12, 15), and diarrhea (20). In the present case, clinical signs of emesis, and loss of appetite increased after antibiotic therapy (three days after treatment onset), while blood in the feces was only reported a day before death (seven days after initial therapeutic approach). Weight loss may have not been documented due the rapid clinical manifestation. Although it was not possible to assure whether the antibiotic therapy was decisive for the development of vomiting, cases of vomit and anorexia have been rarely reported in dogs in use of cephalexin according to the manufacturer, most times associated to cases in which there was a chronic use or an error in the drug dosages (21).

Hypoproteinemia and anemia are described in human beings with Ménétrier disease, and this may be related to protein and blood leakage through the damaged gastric mucosa (3). In the present case, edema and hemorrhage may have been caused by the same mechanisms. Metastatic emboli of the small intestinal mucosal and submucosal lymphatic vessels may have also contributed. Besides metastatic foci, no other significant histologic lesions were seen in the intestinal mucosa. Although chronic renal lesions may have also contributed with protein losing nephropathy and consequent edema (2), the renal lesions were not severe.

The hypertrophic gastropathy is grossly characterized by gastric wall thickening with diffuse increasing of gastric folds forming a "cerebriform" pattern, generally sparing the antral mucosa. Histologically, the disease is characterized by foveolar mucous cells hyperplasia, with gradual replacement and loss of parietal and chief cells, followed by gastric glands dilatation (3). The present condition should be differentiated from another gastropathy named secretory hypertrophic gastropathy (Zollinger-Ellison syndrome) (5, 7). The last is generally presented as a marked parietal cell hyperplasia induced by gastrin, which tends to occur secondarily to pancreatic gastrinoma (15). Lastly, it needs to be differentiated from the chronic hypertrophic pyloric gastropathy, which may also be hormonally influenced, and followed by thickening of the gastric mucosa; however, it tends to be confined to the pyloric region, causing pyloric stenosis and physical obstruction (13). None of these features were observed in our case.

Canine gastric adenocarcinomas tend to appear in 10 year-old (mean onset) animals, arising from the distal portions of the organ, with metastases to the regional lymph nodes and poor prognosis. Its occurrence has been associated with diet components and predisposing hypertrophic conditions (13), such as the one described in this report.

According to the classification proposed for human patients (9), the neoplasm of this particular case would better fit as a mixed-type carcinoma, by sharing some important histological features with diffuse and intestinal types of gastric carcinoma, such as infiltrative individualized cells with mucin production, sometimes interspersed by glandular structures with a central lumen and peripheral polarized cells (9).

In human medicine, the risk of poorly differentiated adenocarcinomas with metastasis arising within hypertrophic gastropathy is always considered (14). A similar pattern was observed in the present case, with a significant metastatic neoplastic spread. Dysregulated receptor tyrosinase kinases (RTK) with overexpression of TGF-alpha (a ligand for the RTK) and mutations of the genes encoding RTK have been associated with the development of both conditions described here, and may explain its simultaneous occurrence (3, 4).

Hypertrophic gastropathy with adenocarcinoma, a condition similar to the gastric hypertrophic condition observed in humans (Ménétrier's disease), should be considered within the differential diagnoses of gastric diseases in small companion animals.

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Declaration of conflict of interests

We have no conflicts of interest to declare.

Authors' contributions

The authors contributed equally to the manuscript.

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