

A Case of Gastric Adenocarcinoma in a Shih Tzu Dog: Successful Treatment of Early Gastric Cancer

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ABSTRACT. A 9-year-old castrated male Shih Tzu dog was referred to us, because of chronic vomiting. The patient's hematological, radiographic, ultrasonographic, endoscopic and histological examinations were evaluated for diagnosis. Hematologic analysis indicated moderate anemia and azotemia. Based on the imaging studies, an oval-shaped mass was identified in the gastric pylorus area. A proliferative mass was found on endoscopic examination, and we performed biopsy using grasping forceps. The histopathological findings of the biopsy specimens indicated hypertrophic gastritis, and Y-U pyloroplasty was performed. However, histopathological examination of the surgically resected mass revealed tubular adenocarcinoma of the stomach. Then, carboplatin chemotherapy was performed 4 times for 13 weeks. Clinical signs, such as vomiting, were resolved gradually after surgery and chemotherapy, and the patient's condition was managed favorably until recently (30 months after surgery). This case report describes clinical features, imaging studies, endoscopic characteristics and histopathological and immunohistochemical features of gastric tubular adenocarcinoma as early gastric cancer in a dog.

KEY WORDS: adenocarcinoma, canine, early gastric cancer (EGC), gastric hyperplasia.

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Tumors of the canine gastrointestinal (GI) tract are uncommon and account for less than 1% of all reported neoplasms [4, 10, 36]. Evidence for the etiology of canine gastric tumor has not been defined until now [10]. Malignant gastric tumors have been reported more than benign tumors, followed by adenocarcinoma, leiomyosarcoma, lymphoma, leiomyoma and adenoma. Adenocarcinoma is the most common gastric malignancy in dogs, comprising 47 to 73% of all gastric tumors [12, 14, 28, 31]. The World Health Organization (WHO) classifies gastric carcinomas in domestic animals, dividing them into 5 types: tubular carcinoma, mucinous carcinoma, signet ring cell carcinoma, undifferentiated carcinoma and papillary carcinoma [13]. The prognosis of adenocarcinoma is mostly guarded, and most studies of this tumor type report that the majority of patients survive less than 6 months [2, 6, 8, 10, 15].

This case report describes clinical features, imaging studies, endoscopic characteristics and histopathological features of canine tubular adenocarcinoma of the stomach in a dog.

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A 9-year-old castrated male Shih Tzu dog presented with a history of chronic vomiting and episodic melena. According to the case history, vomiting sign was observed 8 months before presentation. A GI protectant was administered at a local animal hospital, and no neoplastic changes were found on GI endoscopy. Since moderate anemia (hematocrit: 25%) was identified based on a complete blood count, erythropoietin was given to the patient at the local animal hospital. The patient was referred to us, because the chronic vomiting and anemia were not resolved after management at the local animal hospital. At the time of initial presentation, moderate to severe anemia (hematocrit: 19.6%) and increased alkaline phosphatase and blood urea nitrogen were revealed in a blood analysis (alkaline phosphatase, 743 U/l [reference range; 20-150 U/l]; blood urea nitrogen, 76 mg/dl [reference range; 7-25 mg/dl]). The survey abdominal radiographs showed distension of the stomach, accumulation of gas in the esophagus and a soft tissue opacity mass, which was summated with the gastric pylorus (Fig. 1). Abdominal ultrasonography showed an oval-shaped mass of mixed echogenicity in the gastric pylorus, which was surrounded by thickened muscularis layers and gastric dilation with fluid and food (Fig. 2). In a color Doppler test, the muscularis layers exhibited vascular flow. These gastric changes were considered to indicate a gastric neoplasm.

A gastrointestinal endoscopic examination was performed, and a proliferative mass was found in the pyloric outflow tract (Fig. 3A). Multiple biopsy samples were taken

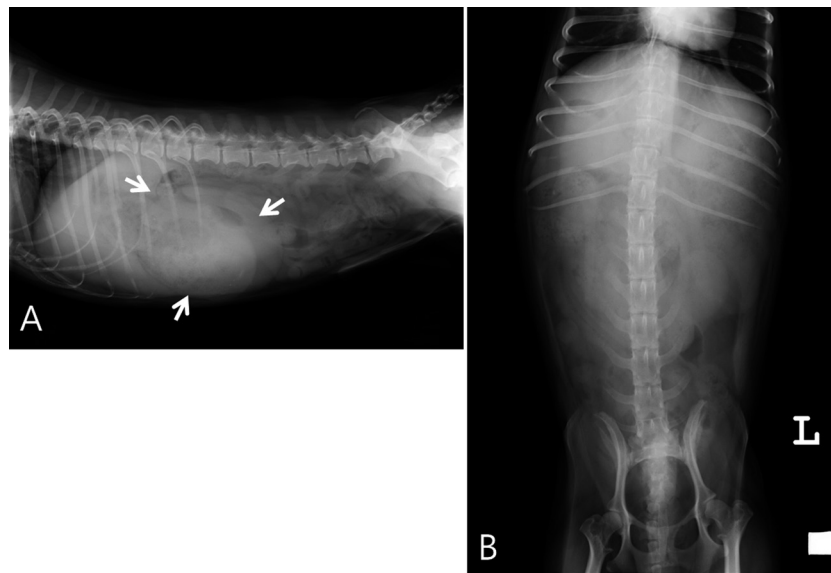


Fig. 1. Survey lateral abdominal radiography shows (A) the presence of a well-defined, smooth, oval-shaped mass with soft tissue opacity overlapped with the stomach caudal to the liver and (B) enhancement of the soft tissue opacity at the cranial and middle regions of the abdomen and distension of the stomach with food, with the stomach deviating laterally and being positioned vertically.

with grasping forceps (Fig. 3B), and the histopathological results for these specimens indicated hypertrophic gastritis (Fig. 5A). Then, we performed marginal resection of the tumor and a Y-U pyloroplasty (Fig. 4). After the surgery, the patient was given partial parenteral nutrition therapy for 10 days, because of vomiting. Eleven days after the surgery, the patient was allowed the liquid food, and clinical signs were gradually alleviated including vomiting and diarrhea.

The histologic results for the surgically resected masses indicated intestinal type (tubular type) gastric adenocarcinoma. The gastric adenocarcinoma was formed by glands with various degrees of differentiation (Fig. 5C and 5D). The gastric lesion was composed of well-formed tubules, some of which were cystically dilated (Fig. 5B). Based on the histopathological findings, we strongly suspected gastric adenocarcinoma. To confirm our tentative diagnosis, we performed additional immunohistochemistry to evaluate the expression of CDX-2 (Abcam, Cambridge, MA, U.S.A.) and Ki-67 (Clone MIB-1, Dako, Glostrup, Denmark). Sec-

tions were placed in a 65°C oven for 20 min, dewaxed and rehydrated through xylene and graded ethanol solutions to phosphate buffered saline (PBS; pH 7.4, 0.1 M). Endogenous peroxidase was blocked by incubating the sections in 3% H₂O₂ in PBS for 20 min at room temperature (RT). After three washes in PBS, antigens were retrieved by heating in citrate buffer (pH 6.0) for 20 min in a microwave oven (650 W at high power). Each section was then overlaid with primary antibodies to CDX-2 (1:200) or Ki-67 (1:300) diluted in PBS. Sections were incubated with primary reagent at 4°C overnight and then washed in PBS three times. EnVision system-HRP (DakoCytomation, Carpinteria, CA, U.S.A.) was applied for detection of binding of primary reagents. Sections were counterstained with Harris's hematoxylin, dehydrated and coverslipped under Permount™ (Fisher Scientific, Fair Lawn, NJ, U.S.A.). Intense nuclear CDX-2 expression was noted in moderately differentiated tumor cells (Fig. 5E and 5F). Moderate expression of nuclear staining for Ki-67 was seen in tumor cells (Fig. 5G and 5H). The

Fig. 2. Abdominal ultrasonography shows (A) vascular flow of the pyloric region in the Doppler test, (B) the presence of thickening of the gastric wall and (C) no pyloric obstruction in postoperative abdominal ultrasonography. (D) Fourteen months after surgery, a decrease in gastric wall thickness can be seen.

Fig. 3. Serial endoscopic findings of the present patient. (A) Obstruction of the pyloric region by a proliferative mass was identified in the initial examination. (B) Several endoscopic biopsy samples were obtained from the lesion. (C) Five months after surgery, occlusion of the pyloric region was resolved. (D) Nineteen-months after surgery, the pylorus was open, and there were no ulcerative or hemorrhagic lesions.

Fig. 4. Resection of the mass and Y-U pyloroplasty. (A) Intraoperative photograph showing the mass at the pyloric region after gastrotomy (arrows). (B) Resection of the mass is complete. The defect was closed by re-positing the mucosa and submucosa with the Cushing pattern. (C) The resected mass of the pyloric area. The margin of the mass, including the mucosa and part of the submucosa layer, was peeled off the pylorus. (D) A completed Y-U antral advanced flap.

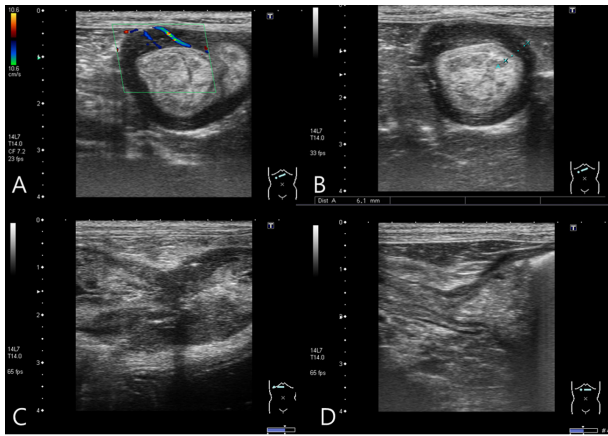


Fig. 2.

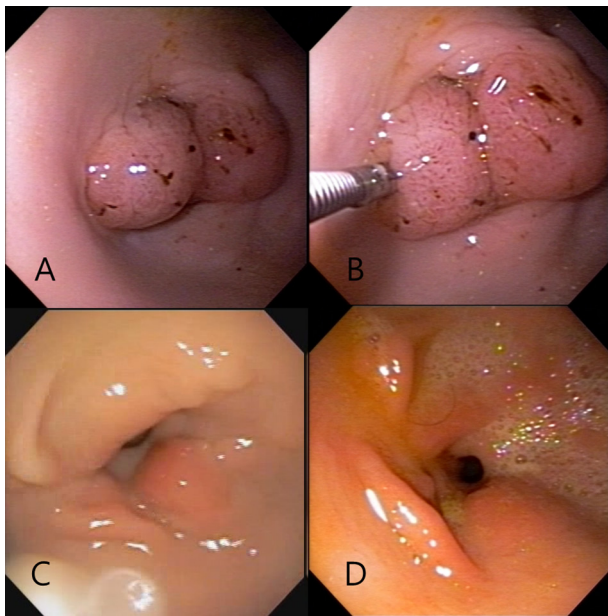


Fig. 3

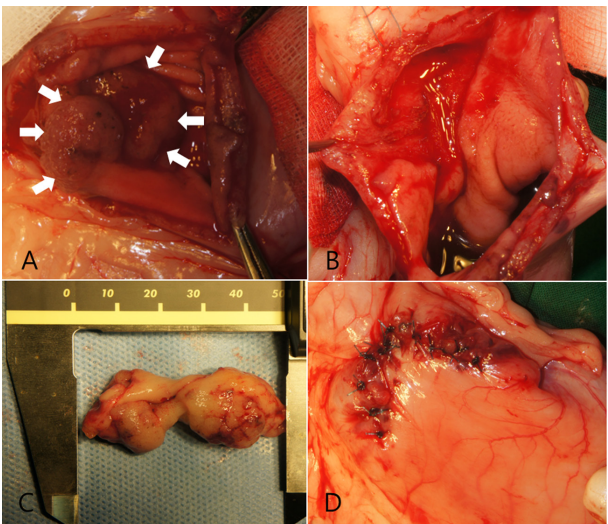


Fig. 4

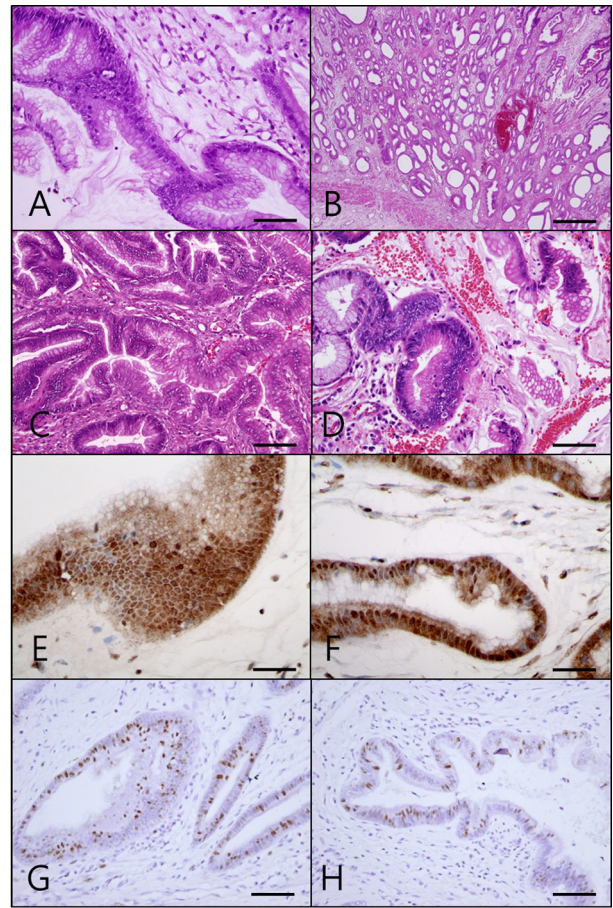


Fig. 5. Histopathological results of endoscopic biopsy specimens (A) and surgically resected specimens (B, C, D, E, F, G and H). Panels A, B, C and D show hematoxylin and eosin staining features. Panels E, F and G show CDX-2 immunohistochemical features of surgically resected specimens. Panel H shows p53 immunohistochemical features of surgically resected specimens. (A) A high power image shows the involved gastric pit (crypts), which contains enlarged hyperchromatic nuclei that became crowded nuclei (scale bar: 32 μ m). (B) The gastric lesion is composed of well-formed tubules, some of which are cystically dilated (scale bar: 467 μ m). (C and D) Intestinal type (tubular type) gastric adenocarcinoma formed by glands with various degrees of differentiation (scale bar: 47 μ m). (E and F) CDX-2 expression in a moderately differentiated tubular type of canine gastric adenocarcinoma. High power images show strong nuclear expressions of CDX-2 in moderately differentiated tumor cells in the present patient (scale bar: 32 μ m). (G and H) Moderate expression of nuclear staining for Ki-67 seen in the present patient (scale bar: 47 μ m).

expression of Ki-67 was partially positive, indicating that the tumor cells had progressed to a malignant form. Based on the histopathological and immunohistochemical findings, this case was definitively diagnosed as an early stage canine gastric adenocarcinoma.

Unfortunately, marginal resection of the tumor and Y-U pyloroplasty had been performed based on the endoscopic biopsy results (hypertrophic gastritis), and we could not be confident that all cancer cells had been removed during the surgery. Therefore, we decided to treat with carboplatin chemotherapy (Carbotinol[®], Korea United Pharm., Seoul, South Korea; 250 mg/m² for the first injection and then 200 mg/m² 3 times during 10 weeks). Then, we regularly performed hematologic, radiographic and ultrasonographic examinations to evaluate the dog for metastasis or recurrence of the cancer. We performed thoracic and abdominal computed tomographic (CT) examinations 2 times after surgery (5 and 11 months after surgery), and the results were normal. Furthermore, gastrointestinal endoscopic examinations were performed again, and there were no remarkable findings (Fig. 3C and 3D). The status of the patient was well controlled until recently (more than 30 months after surgery).

Canine carcinoma is the most common gastric neoplasm in the dog [9, 24]. The WHO classifies this malignancy in domestic animals based on the growth pattern of the carcinoma, but the relation between the histological type and other characteristics associated with the prognosis has not been previously reported [2, 13]. Carcinoma of the canine stomach may arise in any part of the stomach. Canine gastric carcinomas can assume a wide range of forms, but they mostly have the features of tubular adenocarcinoma. This case was a mucosa form and was diagnosed as intestinal type (tubular type) canine gastric adenocarcinoma.

The diagnosis of gastric neoplasms is usually based on clinical features and imaging findings and is confirmed by histopathological and immunohistochemical examinations [19]. Endoscopy is a useful definitive diagnostic investigation for observing the size, location and morphology of a tumor and for obtaining biopsy samples [10, 20]. In humans, over 90% of tumor cases can be diagnosed by endoscopy [14]. In the present case, the histologic result for the endoscopic forceps biopsy specimens was hypertrophic gastritis, but the result for the surgically resected specimens was gastric tubular adenocarcinoma. Interestingly, histologic discrepancies have been reported for gastric cancer between endoscopic forceps biopsy and surgical endoscopic treatment sample in human medicine with the incidence ranging from 25 to 35% [11, 25]. According to one report of human gastric cancer, this discrepancy is found frequently in early gastric cancer (EGC). EGC is defined as adenocarcinoma confined to the mucosa or submucosa, irrespective of lymph node involvement, in human medicine [9]. Because endoscopy cannot detect diseases that primarily involve the submucosal, muscularis or serosal layers of the stomach and the size of the biopsy sample is restricted by the cup size [20], EGC may not be identified with this procedure. Based on these studies, the gastric tumor in the present case could be thought of as equivalent to EGC in humans. The gastric tumor in the

present patient was restricted to the mucosal and submucosal areas, and there was no metastasis to other organs or lymph nodes. Furthermore, there were sessile nodules of mucosal proliferation instead of ulcerative, hemorrhage and infiltrative lesions which are seen in most cases of adenocarcinoma on endoscopy.

CDX-2 is an intestine-specific homeobox product that plays a key role in the regulation, proliferation and differentiation of intestinal epithelial cells during normal embryonic and postnatal development. CDX-2 is known as an important nuclear transcription factor that regulates development of intestinal metaplasia and gastric carcinogenesis [5, 21, 32, 35]. According to previous reports [5, 16, 22, 27, 35], CDX-2 is strongly associated with the intestinal phenotypic expression in gastric carcinomas.

One recent veterinary report [5] demonstrated that all canine gastric adenocarcinomas in the study expressed CDX-2 and that 86.4% of the colorectal adenocarcinomas expressed CDX-2. Interestingly, that report [5] indicated that CDX-2 expression was detected in the normal canine colorectal mucosa, but was not found in the normal canine gastric mucosa. Based on those study results [5], CDX-2 expression could be useful for the diagnosis of canine gastric adenocarcinoma, as it was not detected in the normal canine gastric epithelium. One other report suggested CDX-2 expression was increased in gastric carcinomas with less invasiveness and an intestinal phenotype, but CDX-2 expression was decreased in advanced gastric carcinomas [16]. Strong nuclear expressions of CDX-2 in moderately differentiated tumor cells were noticed in the present patient. However, whether or not CDX-2 is expressed in nonneoplastic conditions, e.g. hypertrophic gastritis, is unknown, although the normal gastric mucosa is almost negative.

Thus, we performed Ki-67 immunohistochemistry as proliferative marker for evaluating malignancy in the present patient. According to previous reports [18, 23], Ki-67 is a nonhistone protein with expression that peaks during G2/M, so tumors with a higher proliferation rate demonstrate greater Ki-67 expression. In the present patient, positive Ki-67 expression was detected in tumor cells, and this suggested a malignant tumor of the gastric mucosa.

Therefore, the immunohistochemistry results for CDX-2 and Ki-67 could support the diagnosis of early stage gastric adenocarcinoma (early gastric cancer) in the present patient.

Surgery is the only potentially effective treatment for localized canine gastric carcinoma [10, 24], and partial gastrectomy is usually indicated for this malignancy [7]. Generally, the prognosis after surgery is poor, and most affected dogs expired within 6 months of diagnosis [3]. In several studies that described the prognosis of surgical treatment for canine adenocarcinoma, the median survival time was only 55 days for 29 dogs treated with surgery. [8, 10, 33]. In human cases, endoscopic submucosal dissection or surgical resection is indicated for EGC [17]. In the present case, we performed surgical submucosal resection of the mass and Y-U pyloroplasty for obstruction of the pyloric outflow tract based on the initial histopathological results. We then initiated chemotherapy since identified malignant change

of the mass. According to one study in humans, adjuvant chemotherapy was effective for prevention of postoperative recurrence in patients with EGC [30]. In human stomach tumor, chemotherapy is effective as an adjuvant therapy followed by surgical resection, improving overall survival [26, 29]. Carboplatin chemotherapy for adenocarcinoma is controversial these days, but carboplatin has been shown to have an antitumor effect in human gastric tumor cells and animal models of gastric tumor [1]. Furthermore, carboplatin had marginal activity in patients with gastric cancer, with response rates of 6–10% as a single agent [29, 34]. In the present case, we used 250 mg/m² carboplatin for the first injection and then used 200 mg/m² for the 3 subsequent treatments. Despite the fact that this type of tumor is known to have a guarded prognosis, the status of the patient has been well controlled after treatment (30 months after surgery).

In conclusion, this report describes the clinical features and prognosis of a canine tubular type gastric adenocarcinoma treated with surgical resection and chemotherapy. We suggest the possibility that a gastric tumor similar to EGC in humans could exist in dogs. This report is the first report of a human EGC-like gastric tumor in dogs. Therefore, more cases of suspected EGC in dogs should be studied in an attempt to investigate this type of tumor.

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