The Regurge Scourge

A Case of Gastric Adenocarcinoma in the Canine Patient

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Introduction

Canine gastric neoplasia is a relatively uncommon manifestation of neoplasia, accounting for approximately 1% of all reported neoplasms in the canine patient (1). Of all the forms of gastric neoplasia, gastric adenocarcinoma is by far the most common, accounting for 60-70% of all cases in the dog (1, 2, 3). Gastric adenocarcinoma is exceedingly rare in cats (3). According to Fossum, "adenocarcinomas arise from tissue or are composed of tumor cells that form glandular structures" (3). Several studies have indicated that male dogs have a higher incidence of gastric adenocarcinoma (2, 3, 4) Most dogs develop this neoplasia between seven and ten years of age but it has been reported in some dogs as young as three (2). Several studies have been conducted to determine if there is a breed predilection to gastric adenocarcinoma. Tervurens, Bouvier des Flanders, Groenendael, collie, standard poodle, Norwegian elkhound, Chow Chows, and the Staffordshire bull terrier are breeds that have been indicated to have a higher prevalence of gastric adenocarcinoma (3, 4, 5). These types of tumors are known to primarily invade the pyloric antrum and lesser curvature of the stomach (3, 4). Gastric adenocarcinomas tend to metastasize, especially to regional lymph nodes, liver, lungs, omentum, pancreas, spleen, esophagus, adrenal glands and duodenum, and are normally not recognized until late in its progression leading to a poor prognosis in most cases (2,3,4).

Dogs with gastric adenocarcinoma normally do not present with clinical signs until late in the disease process (3). Common chief complaints include chronic vomiting, hematemesis/melena, anorexia/weight loss, depression and lethargy, or pain and restlessness (8). Physical examination of dogs with gastric adenocarcinoma may be normal; however, poor body condition, abdominal pain upon palpation, as well as presence of an abdominal mass may be noted (8). In addition, anemia secondary to chronic gastrointestinal bleeding may be present in

the canine patient with pale mucous membranes (8). Due to the nonspecific clinical signs and physical examination findings in patients with gastric adenocarcinoma, advanced diagnostics such as radiography and ultrasonography may aid in the localization of the lesion; however, confirmation of this disease process requires a biopsy, commonly obtained via endoscopy or surgical exploration (8).

History and Presentation

Bailey, a 13 year old female spayed West Highland Terrier, originally presented to the Veterinary Specialty Center (VSC) in Starkville, MS on July 23, 2018, for evaluation of recent development of seizures, circling, and a mass in the brain found on July 16, 2018, via MRI at another hospital. In April of 2018 Bailey began having seizures, which were characterized by lateral recumbency, paddling, and unresponsiveness for 1-2 minutes at a time. Following each episode, Bailey would circle to the right and exhibit abnormal mentation for approximately 10 minutes. Bailey had been presented to her primary veterinarian who prescribed phenobarbital 15mg twice daily. Bailey's seizures would decrease in severity but would still occasionally occur. In early July, Bailey had a cluster of three seizures that lasted 30 seconds each. MRI performed on July 16, 2018, revealed a mass in the frontal lobe of the brain. Her primary veterinarian increased Bailey's phenobarbital dosage to 30mg twice daily and referred to VSC. The owners reported that Bailey had been vomiting about three times weekly when the seizures first began, but has not exhibited any change in diet or water consumption.

Upon presentation to VSC, Bailey was bright, alert, and responsive. She exhibited normal vital signs, and neurologic examination was normal with no neurological deficits. On July 23,2018, Bailey was assessed at Veterinary Specialty Center. After review of her MRI and discussion with her owners, surgery was elected to address the rostral brain mass. A CBC,

chemistry panel, assessment of clotting factors, abdominal radiographs, abdominal ultrasound, and thoracic radiographs were performed. After results of these tests were obtained, Bailey was confirmed to be healthy enough to undergo the procedure.

On July 24, 2018, Bailey underwent a transfrontal craniotomy to debulk the rostral brain mass. Surgery and anesthetic recovery were uneventful. A biopsy was taken of the mass during surgery, revealing it to be a Grade 1 meningioma. After surgery, Bailey was transferred to the ICU and shortly after displayed a propensity to circle to the right which had been a presenting complaint, but had a normal mentation the morning after surgery. Bailey's owners had to go out of town, so they elected to board Bailey in the ICU until their return. Bailey was doing well overall in ICU, but began having episodes of regurgitation infrequently. At this time, a transition to hard food was taking place. Bloodwork was performed revealing a markedly elevated ALP and a mildly elevated total bilirubin, likely secondary to her phenobarbital. At this time the food was changed back to i/d canned and Bailey was started on Cerenia.

Bailey did rather well until August 5, 2018, when she had another episode of regurgitation. On August 6, 2018, a chemistry panel was performed, which still revealed a markedly elevated ALP, but decreased from the previous value. In addition, phenobarbital levels were sent off at this same time. Results revealed Bailey's phenobarbital levels to be in the low-normal therapeutic range. Due to the results of both blood tests it was determined that the elevated ALP value was likely due to the intra-operative use of steroids, and was expected to continue to decrease. Since Bailey's seizures had been well controlled since, no changes to her dose of phenobarbital were be made at this time, but her dose could be increased later if needed. Cerenia was discontinued on August 9, 2018. Bailey had no episodes of regurgitation until the

late hours of August 11, 2018, and she was given an injection of Cerenia and placed back on the oral medication.

Bailey was discharged from MSU-CVM ICU on August 13,2018, on phenobarbital 30mg twice daily as well as hydroxyurea 200mg tablets to be given three times weekly as a chemotherapeutic agent for meningioma. It was recommended that Bailey have bloodwork rechecked in 2-3 weeks at her primary veterinarian and return to VSC in approximately 4 weeks for assessment of her neurological status.

However, on August 31, 2018, Bailey returned to MSU AHC Emergency Service for lethargy and anorexia. Her owners reported that after starting hydroxyurea for chemotherapy for the meningioma on August 20, 2018, a decrease in Bailey's appetite was noted, and she reportedly had not eaten anything since Tuesday August 21, 2018.

Diagnostic Approach/Considerations

Upon presentation to the Mississippi State Emergency Service on August 31, 2018, Bailey was dull but alert and responsive. Temperature, pulse, and respiration were 100.1 F, 80 beats per minute, and 40 breaths per minute, respectively. Bailey's mucus membranes were pink with a normal capillary refill time (CRT) of <2 seconds and her dehydration status was estimated at 7% dehydrated. Pulses were strong and synchronous. Her neurological exam and cardiopulmonary auscultation was within normal limits. Bailey's abdomen was soft and nonpainful, and all peripheral lymph nodes palpated normally. The rest of physical exam was unremarkable. Doppler blood pressures were low around 85 (systolic). An ECG showed a sinus bradycardia. A SNAP cPLI was abnormal, consistent with pancreatitis. A CBC showed moderate neutrophilia and mild lymphopenia, and a chemistry panel revealed markedly elevated ALP and mildly increased CK. Bailey was started on LRS IV fluids, Cerenia, and pantoprazole.

On August 31, 2018, an abdominal ultrasound revealed that the stomach wall was diffusely thickened with loss of normal wall layering, and was distended with fluid. No peristaltic contractions of the stomach were noted. Within the caudal aorta, a partial aortic thromboembolism was seen. There was a small amount of peritoneal effusion and focal peritonitis around the pancreas, and the pancreas was diffusely enlarged and irregularly marginated. Aspirates were taken of the stomach wall and submitted for cytology, which showed macrophagic inflammation. Based on the ultrasound findings, Bailey was presumptively diagnosed with severe pancreatitis and gastroenteritis. A nasoesophageal (NE) feeding tube was placed in the left nostril and secured in place with skin staples. Thoracic radiographs showed an alveolar pattern indicating possible aspiration pneumonia.

Bailey was closely monitored in ICU over the next few days on LRS, a fentanyl CRI, metoclopramide CRI, ondansetron, Cerenia, pantoprazole, clopidogrel, and sucralfate. She began to slowly be fed through her feeding tube with Clinicare. Serial abdominal FAST scans were performed to monitor for stomach and intestinal motility. She continued to regurgitate frequently with no stomach motility observed, and throughout the weekend her condition worsened, as she became increasingly lethargic and dull. A repeated abdominal ultrasound revealed that the stomach was wall had increased from 0.75 cm to 1.3 cm in thickness.

On September 5, 2018 Bailey underwent an upper gastrointestinal endoscopy and biopsies. The endoscopy revealed that the region of the pyloric antrum had an extensive amount of infiltration in the gastric wall and mucosa. The pyloric antrum was nondistensible and the mucosa was inflamed and irritated in this area of the pyloric antrum. Navigation of the area was difficult due to the amount of infiltration. Multiple biopsies were taken from the location of the

affected tissue and were submitted for histopathology. The biopsy results revealed gastric adenocarcinoma.

Pathophysiology

The reason gastric neoplasia develops in the canine patient is largely unknown, although it is believed both genetics and environment play a role (4). Gastric adenocarcinoma, like all other cancers, is a genetic disease that is driven by altered gene expressions and mutations that allow the normal forming cells to become the malignant, disease-causing cells (7). There are generally two types of cancer-associated mutations: acquired and inherited (7). It is believed that the inherited cancer predisposition may play a much larger role in dogs than in humans, since there are such strong breed predilections between certain breeds and certain neoplasias (7). Some breeds such as the Chow Chow have been shown to have 10-20 times increased risk of gastric carcinoma, tending to back the argument of heritable cancer predisposition (7). Most genetic mechanisms associated with low to moderate risk of developing gastric adenocarcinoma have been associated with polymorphisms in genes coding for mediators of inflammation (7). Several factors have been implemented as a potential cause for gastric adenocarcinomas in human medicine, and now have been indicated in veterinary medicine, such as E-Cadherin, DNA mismatch repair, *Helicobacter* infection, and expression of CDX-2, HER-3 (7, 9).

E-cadherin is described as a glycoprotein that mediates calcium-dependent intercellular adhesion (7). This glycoprotein is essential in maintaining organization and polarity of epithelial surfaces. Mutations in the CDH-1 gene, which are responsible for encoding E-cadherin, have been associated with a greater than eighty percent chance of developing diffuse gastric

carcinoma. The prevention of widespread gastric carcinoma growth in these cases have been prophylactic gastrectomy, which have revealed microscopic foci of carcinoma in grossly normal samples (7).

A second point of interest as what could be the cause of gastric adenocarcinomas is a defect in the DNA mismatch repair machinery (7). DNA mismatch repair machinery is responsible for maintaining the integrity of the genome and, if there is a defect, a microsatellite instability can be created. These microsatellite instabilities have been associated with hereditary nonpolyposis colon cancer since the 1990's. The association between the microsatellite instabilities and the nonpolyposis colon cancer lead researchers to identify four different defective DNA mismatch repair machinery sites that can predispose individuals to cancer. It is believed that the mutations in these genes that contain these defective repeats lead to carcinogenesis. There is a strong correlation between individuals with colon cancer being at an increased risk of developing gastric cancer as well. Tissue specificity of defective mismatch repair machinery is poorly understood but could prove to be a factor in the development of canine gastric adenocarcinoma (7).

Studies performed in humans have shown that those infected with *Helicobacter pylori* are at an increased risk of development of gastric neoplasia, as certain virulence factors in *Helicobacter* and the individual response to the inflammation can each play a role in the development of gastric neoplasia (6). However, in the canine species, there is no evidence that infection with *Helicobacter pylori* leads to gastric adenocarcinoma as it is a very common inhabitant of the gastrointestinal tract, yet the incidence of gastric adenocarcinoma in the dog is low (6). Even though there is no real evidence that *Helicobacter* directly causes gastric adenocarcinoma development in dogs, the inflammatory response and role of mediators in

inflammation leading to an increased susceptibility to the development of adenocarcinoma is an interesting topic (7). *Helicobacter pyogenes* is associated with being a common cause of gastric ulcers in humans and in dogs. Gastric carcinoma has shown an association with COX-2, Glutathione-s-transferase, and IL1B in humans but the relationship is only thought to marginally increase the risk of adenocarcinoma (7).

CDX-2 is another potential cause of gastric adenocarcinoma. CDX-2 is described as a nuclear transcription factor of the caudal homeobox family, which plays a vital role in the regulation, proliferation, and differentiation of intestinal epithelial cells during normal embryonic and post-natal development (9). This nuclear transcription factor also regulates the development of intestinal metaplasia and gastric carcinogenesis. Studies have also shown that *in vivo* CDX-2 is important in early differentiation and maintenance of intestinal epithelial cells. It has proven to be a reliable marker for detection of human intestinal adenocarcinomas, colorectal cancer, and metastases. A study in 2011 sought to find the relevance of the expression of CDX-2 in canine colorectal and gastric adenocarcinomas. The study revealed that all of the gastric adenocarcinomas and 84.6% of the colorectal adenocarcinomas expressed CDX-2. Furthermore, CDX-2 was only found in animals with abnormal gastric mucosa, but it was also found in dogs with normal and abnormal colorectal mucosa (9).

HER-3 is a transmembrane glycoprotein molecule that consists of an extracellular ligand-binding domain and an intracellular domain with tyrosine kinase activity that have been shown as being important in the development of cancer (9). HER-3 has less tyrosine activity than the other HER transmembrane glycoproteins, so when it is overexpressed it is a good indication of various human cancers such as breast, lung, pancreas, colon and stomach cancer, and metastases. A study in dogs showed that HER-3 was not detectable in normal gastric or

colorectal mucosa, but was elevated in these tissues when adenocarcinoma was present. The study points out that HER-3 could be used to distinguish between neoplastic and non-neoplastic tissue in the gastrointestinal tract in the future (9).

Human medicine has a much more defined pathophysiology for gastric carcinoma than veterinary medicine. In human medicine there are two basic types of gastric carcinoma, intestinal and diffuse type (10). The intestinal type is ill-defined, frequently ulcerates, and arises from precancerous lesions such as gastric atrophy and intestinal metaplasia. The intestinal type is heavily influenced by environmental factors such as *H. pylori* infections, dietary factors, and obesity. The diffuse type is more infiltrative and seems to have a genetic component related to blood type A. Invasive gastric carcinoma involves an evolution from precancerous lesions, histopathological changes in the gastric mucosa including atrophic gastritis with a loss of parietal cell mass, intestinal metaplasia, and dysplasia that eventually leads to carcinoma (10).

Treatment and Management

The results of the biopsy and findings of the endoscopy lead Bailey's owners to elect humane euthanasia, so no treatment for the gastric adenocarcinoma was undertaken. If treatment would have been pursued there are several options that could have been tried. The only potentially curative treatment for gastric neoplasia is surgery (3). Even though surgery is normally the best option, sometimes when the carcinomas are so far advanced (as in this case) they are unresectable (3). In many cases, the gastric adenocarcinoma will cause a gastric outflow obstruction which will cause vomiting and regurgitation (5). When the surgery is undertaken, the post -gastric outflow problem will normally be resolved (5). Most owners elected to euthanize within 10 months of the surgery due to poor quality of life and return of clinical signs (5). Partial gastrectomy is usually indicated in cases of gastric adenocarcinoma (1). Prognosis after surgery

remains poor with survival time being around 6 months (1). Chemotherapy has been shown to be an effective adjunctive treatment with surgery (1). A recent case report suggested that carboplatin may be a useful chemotherapy treatment, as the patient that received it after surgery survived for 30 months (1). Other suggested chemotherapy treatments include 5-fluorouracil, cyclophosphamide, doxorubicin, and cisplatin (11). Chemotherapy for gastric adenocarcinoma is not well understood, and surgical removal of the neoplasia is still the treatment of choice.

Case Outcome

Following the discussion of Bailey's biopsy results, which revealed gastric adenocarcinoma, her owners elected humane euthanasia due to the grave prognosis. Her owners consented to necropsy with cremation to follow. Necropsy performed by MSU-CVM pathologists revealed that the gastric adenocarcinoma had metastasized quite aggressively throughout her body, with the gastric lymph nodes, adrenal glands, lungs, spleen, and bone marrow showing evidence of metastasis.

There was marked fibrosis of the stomach, which likely severely impaired Bailey's gastric function. Approximately 40% of the stomach exhibited marked mural thickening along the fundus and through the pylorus with white foci throughout the serosa. This area of the gastric wall was firm, with a thickness that was 5 times normal. The gastric mucosa in this thickened region had a large, irregular ulcer, which measured approximately 5cm in diameter. Cytological examination of the thickened section of the stomach revealed that the neoplastic foci multifocally were noted in the deep mucosa, however, they rarely reached the superficial mucosa and were surrounded by hyperplastic lymphoid tissue and mesenchymal proliferation. Nests of neoplastic cells were embedded within thick, desmoplastic stroma, within ectatic, or dilated, lymphatics peppered throughout the muscularis layers. The neoplastic cells were characterized as being

large, round, and demonstrate distinct borders with a large amount of eosinophilic cytoplasm. Multiple nuclei frequently were noted within one cell, with chromatin marginated or finely stippled and 1-3 frequently prominent magenta nucleoli. The neoplastic cells were described as frequently containing one to multiple clear vacuoles, which contained mucinous material and caused peripheralization of the nuclei. A variable mitotic rate was described with roughly up to 5 per high powered field, with marked anisocytosis as well as anisokaryosis. These neoplastic cells were also reported to have been seen in gastric lymph node, adrenal gland, lungs, liver, spleen, and bone marrow. Gastric pits were multifocally thickened and irregular and necrosis was abundant within the lymphatic emboli.

The lymphoid architecture of the gastric lymph node examined was diffusely effaced by the same neoplastic cells described in the stomach, and was surrounded by a desmoplastic stroma. Vessels in this area were markedly distended, and contained clusters of these neoplastic cells, which sometimes surrounded nerves.

Grossly, the lungs appeared normal and were mottled dark red/red. The lungs revealed moderate to severe, subacute, disseminated pulmonary edema as well as hemorrhage. The neoplastic foci described in the stomach were randomly scattered in variably sized aggregates within ectatic, or dilated lymphatics in the lungs. Vessels were multifocally occluded by thrombi as clumps of fibrin, adhered to the endothelium, and were often mixed with mixed leukocytes and entrapped blood. The alveolar spaces were filled with a small number of plump alveolar macrophages and the alveolar septal capillaries were diffusely hyperemic, with scattered foci of mineralization and small numbers of megakaryocytes noted. The perivascular spaces were multifocally expanded by edema.

Cytological examination of the liver revealed dilated lymphatics, located circumferentially around the central veins as well as within portal tracts of the liver, filled with clusters of the same neoplastic cells described in the stomach. Sinusoids were diffusely expanded by blood, with multifocal small aggregates of bone marrow precursor series present. The portal tracts exhibited multifocal mild to moderate fibrosis with occasionally dilated bile ducts which contained orange to brown bile, which was mixed with a small amount of sloughed bile epithelium. Hepatocytes had variation in cell size, as well as nuclear size, with several being bi-nucleated and containing clusters of clear vacuoles. Diffusely, Ito cells were hyperplastic.

The spleen was pale and exhibited tan to grey plaques along the margins of its head. Large foci of the aforementioned neoplastic cells, surrounded by substantial desmoplastic stroma, focally expanded the splenic parenchyma and extended beyond the capsule within lymphatics. The white pulp of the spleen was inapparent and diffusely depleted of lymphocytes while the bone marrow was roughly 40% cellular with a M:E: ratio of 5:1 with the same neoplastic cells described in the stomach being mixed with the bone marrow cells.

Changes to the kidneys, parathyroid glands, as well as mitral valve were noted on necropsy; however, none of these were directly correlated with the disease process being discussed.

Due to the findings on necropsy, humane euthanasia appears to have been the proper treatment for Bailey due to the extensiveness of the disease.

This case serves as a reminder that a persistent symptom such as regurgitation should not be ignored, and should be investigated as it could uncover a deeper issue. In Bailey's case regurgitation was due to decreased gastric motility from the gastric adenocarcinoma. This was the first clinical sign related to this disease process that was apparent for some time. Proper

standard of care was provided for Bailey in preparing her for her meningioma surgery including an abdominal ultrasound, thoracic radiographs, and abdominal radiographs, but the disease process was not detectable at this time

References

1. Lee HC, Kim JH, Jee CH, et al. A case of gastric adenocarcinoma in a Shih Tzu dog: successful treatment of early gastric cancer. *J Vet Med Sci*. 2014;76(7):1033-8.
2. Seim-Wikse T, Jörundsson E, Nødtvedt A, et al. Breed predisposition to canine gastric carcinoma--a study based on the Norwegian canine cancer register. *Acta Vet Scand*. 2013;55(1):25. Published 2013 Mar 21. doi:10.1186/1751-0147-55-25.
3. Fossum, T.W.(2013). *Small Animal Surgery (4th edition)* St. Louis, MO. Elsevier Mosby. Pg (494-497)
4. Hugen S, R.E. Thomas, A.J. German, I.A. Burgener, P.J. Mandigers. Gastric carcinoma in canines and humans a review. *Veterinary & Comparative Oncology*.2017:15(3): (692-705)
5. Swann Heather M.and David E. Holt (2002) Canine Gastric Adenocarcinoma and Leiomyosarcoma: A Retrospective Study of 21 Cases (1986–1999) and Literature Review. Journal of the American Animal Hospital Association: March/April 2002, Vol. 38, No. 2, pp. 157-164.
6. Shell Linda, Kari Rothrock. Gastric Neoplasia. 1/19/2012. VIN.
7. MnNeil, Elizabeth. Contribution of Genetics to the Pathophysiology of Gastric Adenocarcinoma. ACVIM 2007. VIN.
8. Cote,Etienne. (2011). *Clinical Veterinary Advisor*. *Dogs and Cats*. (Second Edition). St. Louis, MO. Elsevier Inc. Pgs (906-908).
9. A.R.DosterJ.,Y.Yhee,J-H.Kim,K.S.Im.J.H.Sur. CDX-2 and HER-3 Expression in Canine Gastric and Colorectal Adenocarcinomas. Journal of Comparative Pathology Volume 145, Issue 1, July 2011, Pages 12-19
10. Nagini S. Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. *World J Gastrointest Oncol*. 2012;4(7):156-69.
11. Rassnick, Kenneth. From Top to Bottom: Canine Gastrointestinal Tumors. World Small Animal Veterinary Association World Congress Proceedings, 2007.