Canine Small Intestinal Polypoid Adenoma with Transition to Invasive Adenocarcinoma

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Introduction

Although not nearly as common as colonic tumors, small intestinal tumors do occur in both dogs and cats[4]. While lymphoma is the most common in dogs, adenocarcinoma and leiomyosarcoma are the two most common nonlymphomatous, small intestinal neoplasias[4]. Adenocarcinomas, or neoplasms that develop in the lining or inner surface of an organ and usually have secretory properties, can occur anywhere along the gastrointestinal tract of small animals[5,9]. Small intestinal carcinomas are less common than colonic or rectal tumors, and they typically develop as solitary intestinal masses with a propensity to quickly metastasize to regional lymph nodes[4]. Common clinical signs associated with intestinal carcinomas are anorexia, vomiting, diarrhea, weight loss, obstruction, gastrointestinal bleeding, and/or intussusception[8]. Singular adenomatous polyps have been reported solely in the large intestine, and their transformation to malignancy is rare[7].

History and Presentation

Molly Cutie, a 6-year old female spayed Labrador retriever, was presented to Hurricane Animal Hospital in Hurricane, WV on June 12th, 2017 for a 3 day history of lethargy and anorexia. She had been progressively losing weight since April 2015, at which time she had a body condition score of 5/9 and weighed 48.7lbs. She weighed 42lbs on March 3rd, 2017, and although the weight loss was concerning to both the veterinarian and the owners, she was doing well at home and diagnostics were not pursued at that time.

On June 5th, 2017, she presented for a senior bloodwork panel and urinalysis, at which time she weighed 40.4 lbs. The bloodwork showed a hypoalbuminemia of 2.5g/dL (2.7-4.4), a

low total protein of 4.6g/dL (5.0-7.4), and a high ALT of 189 IU/L (12-118). Also, calcium was mildly decreased at 8.8 mg/dL (8.9-11.4) and amylase was high normal at 1120 IU/L (290-1125). Urine was obtained via cystocentesis; the urinalysis revealed 2+ blood, and 2-3 calcium oxalate dihydrate crystals.

With these results, the primary rule-out for Molly Cutie was a protein-losing enteropathy, more specifically lymphangiectasia. Abdominal imaging was recommended to rule-out neoplasia and pursue diagnosis of a possible urolith, along with initiation of empirical treatment. Lymphangiectasia, a condition defined by dysfunction and marked dilatation of intestinal lymphatics, can cause hypoproteinemia with or without diarrhea[1]. This occurs via diseased lymphatics leaking protein-rich lymph into the intestinal lumen and can be a primary or secondary disorder, the latter of which results from lymphatic obstruction[1].

Significant weight loss and lethargy, along with hypoalbuminemia and hypoproteinemia, were the prominent signs exhibited by Molly Cutie that were consistent with lymphangiectasia. This was further reinforced by the patient's long-term, slow weight loss prior to presentation; dogs afflicted with lymphangiectasia often exhibit clinical signs with a slow onset or do so intermittently[1].

A few days after her bloodwork appointment, Molly Cutie began vomiting at home and stopped eating. She was given Cerenia as an outpatient medication until the owners could bring her in on Monday, June 12th for an exam. The Cerenia was ineffective and she continued to vomit intermittently.

Upon presentation, Molly Cutie was dull and depressed and severely cachectic. She weighed 32.6 lbs (nearly an 8-lb decrease from the week before) with a body condition score of 1/9. Her body temperature was low normal at 98.9°F. Thickened loops of bowel were appreciated upon abdominal palpation. All other physical exam parameters within normal limits.

In cases of lymphangiectasia, diet change by way of control of nutrient percentages and immunomodulation via glucocorticoids are primary aims of treatment[1]. Likewise, correction of Molly Cutie's bloodwork abnormalities, namely her hypoproteinemia and hypoalbuminemia, were key in her therapeutic plan.

Thus, Molly Cutie was hospitalized and given 300mls of 6% Hetastarch intravenously over 8 hours. She was started on both dexamethasone 6mg IV every 12 hours and chlorambucil 2mg tabs orally once daily for immunosuppression, and subcutaneous Cerenia injections once daily. Furthermore, she was prescribed 7mg of aspirin orally once daily as an anticoagulant due to lymphangiectasia's association with Vitamin K deficiency[2]. After the Hetastarch bolus was given, her intravenous fluids were switched to a 5% Dextrose solution of LRS supplemented with 1ml of Vitamin B12 added to the bag at two-times maintenance (75ml/hr). She was offered Royal Canin Gastrointestinal Low Fat Veterinary Diet due to its ultra-low fat content coupled with its relatively low fiber content. This is an important balance in diets used to treat PLE in that they should be low in fat while simultaneously being highly digestible and palatable[1]. She was also offered hard-boiled egg whites for additional protein supplementation.

Molly vomited and had very watery diarrhea overnight. On the morning of June 13th, her weight had increased to 34.8lbs (a 2 lb increase from the day before), her fluid rate was decreased to her maintenance rate of 40ml/hr due to adequate hydration and a course of metronidazole was started. Her PCV was 32% and her total protein was 5.0 g/dL, which was an improvement from her TP one week prior (4.6 g/dL). She was also started on 3mg of ondansetron IV every 8 hours as an additional anti-emetic. By the evening her appetite had returned and she was eating the prescription diet and egg whites.

On June 14th (day 3 of hospitalization), her weight had now reached 37.9 lbs, more than a 5-lb increase in 48 hours. She was now bright, alert, and responsive. Firm bowel loops were still palpable but they were not as turgid as they had been upon presentation. At this time, intravenous fluids were discontinued and Molly Cutie's catheter was removed. Her dexamethasone was discontinued and she was prescribed prednisone 20mg tablets – 1 tablet orally once daily for 30 days as well as oral ondansetron. Her total protein was 6.2 g/dL, well within the normal range.

On June 15th (day 4 of hospitalization), Molly Cutie's condition remained stable without intravenous fluids and medications. Aspirin was discontinued and oral Cerenia was started in lieu of subcutaneous administration. Although she had drastically improved clinically, her bloodwork showed an albumin of 2.1 g/dL and a total protein of 4.3 g/dL (compared to an albumin of 2.5 g/dL and total protein of 4.6 g/dL on June 5th). Additionally, a mild hypoglobulinemia was present (2.2g/dL).

Despite the abnormalities present on bloodwork, Molly Cutie was discharged on June 15th with instructions to continue oral medications as prescribed (Cerenia, metronidazole, chlorambucil, ondansetron, and prednisone), as well as her prescription diet and hard-boiled egg whites. A fecal alpha-1 proteinase inhibition test to confirm and quantify the patient's protein-losing enteropathy was recommended but declined by the owners.

At her recheck on June 22nd, Molly Cutie's owners reported that she was doing well at home. She was eating and drinking normally, although she did have intermittent soft stools and her weight had decreased to 34.4lbs. She had finished the courses of Cerenia, ondansetron, and metronidazole but was still taking the prednisone and chlorambucil as prescribed. Her bloodwork had not changed significantly since discharge; hypoalbuminemia, hypoproteinemia, and hypoglobulinemia were all still present. Thickened bowel loops were still present upon abdominal palpation. Molly Cutie was given an injection of Vitamin B-12 and restarted on Cerenia and metronidazole. Due to her weight loss since discharge and continued hypoproteinemia, subcutaneous dexamethasone injections were started in lieu of prednisone with the hopes that this would be more effective.

In the following days, Molly Cutie's condition was beginning to decline again as her appetite and activity level started to decrease. The plan was to initiate total parenteral nutrition after placement of a jugular catheter on Monday, June 26th. Over the weekend prior, however, Molly Cutie decompensated greatly, and she was euthanized Monday morning.

With owner consent, a cosmetic necropsy was performed immediately following euthanasia. Three discrete, polypoid masses varying in diameter from approximately 2-4cms

were found in the proximal half of the jejunum. The oral half of the jejunum was dilated with hyperemic mucosa. Halfway through the jejunum, a firm annular ring was present, greatly reducing the diameter of the lumen. Aborally from the stricture, the small intestinal serosa and muscularis were thickened, although the mucosa appeared grossly normal. The rest of the necropsy was unremarkable. Samples of all level of the gastrointestinal tract, as well as samples of liver, spleen, pancreas, and mesenteric lymph nodes, were submitted for histopathology.

Histologically, the polypoid masses were revealed to be adenomas. The report stated that "the cells [of these masses] are cuboidal to columnar with moderate eosinophilic cytoplasm and small round to ovoid basally located nuclei with marginated chromatin and a single prominent nucleolus." The firm, annular ring was consistent with an invasive, mucinous adenocarcinoma in that it appeared as "…an invasive and infiltrative mass composed of cells arranged in nests and tubules in a fine fibrovascular to scirrhous fibrous connective tissue stroma … The neoplastic cells frequently surround large dilated structures that are filled with abundant mucin."

Most notably, the tissue adjacent to one of the polyps exhibited pre-neoplastic changes consistent with the early stages of transition from benign adenoma to adenocarcinoma. In this area, cells at the base of the intestinal crypts showed dysplastic changes (i.e. the presence of vesicular nuclei and multiple nucleoli) with these abnormal cell lines beginning to invade between the mucosa and muscularis mucosa.

Just as the transition from adenoma to pre-neoplastic cell lines is visible, the transformation of the same pre-neoplastic cells to malignant neoplasia is observed at the outer

margin of the fusiform adenocarcinoma. This is histologic evidence of complete malignant transformation resulting in the invasive adenocarcinoma, as well as early evidence of an additional transition from adenoma to adenocarcinoma occurring at the base of one of the polyps.

Pathophysiology

Carcinomas, or neoplasms arising from epithelial cells, can occur anywhere in the intestine of small animals[8]. Thought to arise from epithelial crypt stem cells, these tumors can be differentiated based on their histologic characteristics; the prefix "adeno" is added to indicate secretory or glandular properties, "mucinous", "signet ring", and "undifferentiated" or "solid"[6,3]. Adenocarcinomas typically arise as discrete masses with a high rate of metastasis to regional lymph nodes[8]. Further classification schemes exist, such as gross appearance and behavior or the neoplasm. Adenocarcinomas can occur as plaque-like and ulcerated masses or they can invade the adjacent small intestinal wall causing a stricture or annular obstruction[3].

In dogs, the colon and rectum are both more common sites for adenocarcinoma than the small intestine[9]. Likewise, benign adenomatous polyps have been reported in both the rectum and colon of dogs, but never in the small intestine[9]. These lesions tend to be solitary masses as well, although they can be diffuse[9]. Transformation of these rectal and colonic polypoid adenomas to adenocarcinoma is reported but rare in dogs[5,6].

Molly Cutie's case is unique in not only the number and location of the adenomatous polyps (three in the jejunum) but also in the malignant transformation of a small intestinal adenoma to invasive, annular, mucinous adenocarcinoma. This type of adenocarcinoma has

been reported in the jejunum of cats and the duodenum and colon of dogs[9]. Nowhere in the available scientific literature is there a report of canine small intestinal adenocarcinoma originating histologically from an adenomatous polyp, singular or numerous.

In humans with familial polyposis syndromes, a mutation in the adenomatous polyposis coli gene leads to a nonfunctional protein, the first step in the multistage progression from benign polyp to carcinoma[5]. It is worth considering that this patient could have had a similar genetic mutation, leading to the multiple polyps and a malignant transformation to adenocarcinoma.

Diagnostic Approach/Considerations

Hypoproteinemia is one of the most common biochemical abnormalities seen in small animals with intestinal tumors[9]. Elevated liver enzymes may also be seen, specifically ALP, which has been reported to be increased in 15-33% of dogs with nonlymphomatous neoplasia[9]. Anemia is also a common finding and attributable either to gastrointestinal bleeding or that of chronic disease[4,6,9]. Elevated BUN, increased amylase, and electrolyte disturbances have all been reported to a lesser extent in dogs with intestinal adenocarcinoma[9].

Molly Cutie's bloodwork results from her June 5th visit exhibited many of these abnormalities, namely hypoproteinemia, hypoalbuminemia, and an increased amylase and ALT. Although neoplasia was not the primary rule-out for this case, the lab results coupled with the patient's clinical signs led to the recommendation to continue pursuit of a diagnosis via abdominal radiographs and ultrasound. Survey radiography can show dilation of the bowel proximal to annular, infiltrative malignancies, like what was seen in this case[6]. Contrast

radiography can be useful in elucidating the narrowing of the lumen present at the tumor site[6,9]. However, ultrasonography is currently the most effective modality for diagnosing canine intestinal tumors. Abdominal ultrasounds in these cases can often reveal transmural wall thickening of the intestine with complete loss of normal wall layering at the tumor site, as well as a regional or local lymphadenopathy and intra-luminal fluid accumulation secondary to obstruction caused by the tumor[6]. Ultrasound-guided biopsy or fine needle aspirate of the masses is often sufficient for accurate diagnosis[6].

Imaging was not pursued in this case due to the rapid decompensation of the patient prior to scheduling a full diagnostic work-up. Radiography and ultrasonography were always diagnostic options offered to the owners, but stabilizing Molly Cutie took precedence, thus they were not performed. Response to therapy, although palliative, while in hospital and shortly after discharge further obscured the need for abdominal imaging.

Treatment and Management

The treatment for small intestinal adenocarcinoma is surgical excision with a wide resection and anasthamosis[4]. Approximately 5cm of normal bowel should be removed on either side of the tumor and the corresponding mesentery should be widely resected as well[4]. Information on prognosis following excision is limited, although the presence or absence of metastasis is a significant prognostic indicator[8].

In a study of five dogs that underwent excision of small intestinal carcinomas, mean survival time was 55 days[4]. In other studies, mean survival time was 12 days without treatment

and 114 following surgery[5]. Chemotherapy in conjunction with surgical excision is reasonable but palliative and not known to affect survival time[5,8].

Mesenteric lymph nodes are the primary site for metastasis, followed by the liver[5]. Confounding factors like metastasis, peritonitis, or the presence of non-resectable tumors leading to an owner decision for euthanasia lead to a perioperative mortality rate that is estimated to be as high as 50%[5].

The adenomatous polyps, while benign, could possibly have been causing partial intestinal obstructions, as evidenced by this patient's steady, slow decrease in weight in the years prior to presentation. Considering the histologic signs of early malignant transformation adjacent to one of the polyps, as well as the lack of documentation of such a presentation in dogs, surgical excision in the manner described for adenocarcinoma would have been a reasonable treatment choice.

Case Outcome

Unfortunately, Molly Cutie's decompensated clinical condition made euthanasia a humane and warranted case outcome. The fact that no metastases were found could be attributed to the quick onset of Molly Cutie's clinical decline, presumably correlated to the transition of benign neoplasia to infiltrative malignancy, effectively acting as a small intestinal obstruction. Molly Cutie was a poor surgical candidate because of her cachexia and bloodwork abnormalities (specifically hypoproteinemia and hypoalbuminemia). Furthermore, invasive annular intestinal adenocarcinoma like the kind seen in this case is associated with one of the lowest mean survival times for dogs with nonlymphomatous gastrointestinal neoplasia[4,7].

This case is unique not only in that three adenomatous polyps were located within the jejunum, but also that transition from adenoma to invasive small intestinal adenocarcinoma was seen. An interesting consideration is that a familial genetic mutation could have been present in Molly Cutie contributing to this tumor transformation, although this would be impossible to confirm at this point. Although Molly Cutie's presentation was unusual, small intestinal neoplasia should be considered as a possible rule-out for any middle-aged or older dog presented for chronic vomiting, weight loss, anorexia, and diarrhea[4].

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