SURGICAL MANAGEMENT OF COLONIC ADENOCARCINOMA IN A RAT (*RATTUS NORVEGICUS*)

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Abstract

A 9-month-old female Dumbo rat (*Rattus norvegicus*) was evaluated for a 24-hour history of obstipation. A general physical examination revealed a large irregular abdominal mass, extending caudally from mid-abdomen to the pelvis. The mass had a firm central region with a compressible periphery. Radiographic imaging confirmed severe intestinal distention, but failed to delineate a discrete mass. Following 3 days of unsuccessful medical therapy for possible colonic impaction, surgical intervention was elected. A colocolic resection and anastomosis was completed to remove 7 cm of the colon, including the 5 cm mass and 1 cm of grossly normal appearing colon proximal and distal to the mass. Histology confirmed colonic adenocarcinoma. The rat lived for 2 years, following colonic resection and anastomosis, uncomplicated by gastrointestinal neoplasia or metastatic disease and was euthanized due to unrelated quality of life issues. Necropsy revealed no evidence of colonic tumor recurrence or metastatic disease.

Key words: rat; *Rattus norvegicus*; adenocarcinoma; subtotal colectomy; cancer

A 9-month-old female Dumbo rat (*Rattus norvegicus*) was presented for clinical evaluation with a 24-hour history of obstipation. The rat was housed with 3 age and sex-matched cagemates in a large wire-mesh paper-lined cage. The diet was pelleted rat food (Essentials—Adult Rat food, Oxbow Animal Health, Murdock, NE USA) and occasional fruit and vegetable treats with water provided in plastic or glass lick bottles. Latrine sites were cleaned regularly and the cage was sanitized weekly with disinfecting wipes and soap and water. Other than obstipation, no other medical problems were noted at presentation.

The rat weighed 320 g and was quiet, active, and responsive on presentation. Physical examination revealed a large irregular abdominal mass extending from mid-abdomen to the pelvis, with a firm central region and compressible periphery. Anesthesia with isoflurane (Primal Enterprises Limited, Andhra Pradesh, India) via chamber induction (5% isoflurane, 5 L/minute oxygen) followed by mask anesthesia (1.5% to 2.5% isoflurane, 3 L/minute oxygen) was performed to complete diagnostic testing.

Right lateral and ventrodorsal radiographic images revealed severe intestinal distention with both gas and heterogeneous stippled soft tissue and gas opaque ingesta. The small intestines and colon could not be distinguished from one

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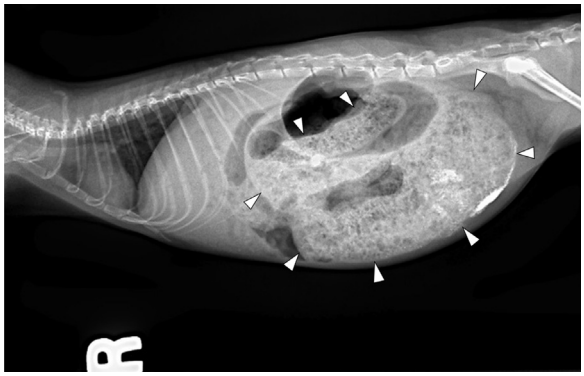

FIGURE 1. Right lateral projection radiograph of a rat (*Rattus norvegicus*). Arrows outline distended large bowel containing heterogenous soft tissue and gas opacity material creating intestinal distention and decreased serosal detail. Mineral density material is seen in the caudal abdomen, possibly in the ingesta or mineralization within the neoplastic tissue.

another and the intestinal distention was too extensive to represent colon alone but a discrete mass could not be identified. Intestinal distention caused cranial displacement of the liver, stomach, and small intestines, a secondary decrease in abdominal serosal detail, and marked abdominal distention, best identified in the lateral projection (Fig. 1). Blood was collected from the left lateral coccygeal vein and submitted for a complete blood count and serum biochemistry panel (Avian & Exotic Animal Clin Path Labs, Wilmington, OH USA). Abnormal results from the complete blood count and serum biochemistry were a leukocytosis with relative monocytosis and elevated alkaline phosphatase (Table).

The first 24 hours of treatment included lactated Ringer's solution (LRS) 25 mL/kg, subcutaneously every 12 hours; buprenorphine 0.1 mg/kg, subcutaneously every 12 hours (Hospira, Rocky Mount, NC USA); and syringe feeding with 9 mL liquid critical care diet every 12 hours (Emeraid Omnivore, Lafeber Company, Cornell, IL USA). The rat's appetite remained excellent, though no feces were produced, and there was no change in the size or consistency of the mass. The second day of treatment included the addition of lactulose 0.25 mL/kg, orally every 12 hours (Hi-Tech Pharmacal Company, Incorporated, Amityville, NY USA) and a combination warm water and surfactant enema completed with the patient anesthetized as described above. The enema only produced the same amount of clear fluid that was introduced with no feces. On the third day of hospitalization, the rat's appetite remained normal, no feces were produced, and the abdominal mass remained unchanged. Additional diagnostics, to include compression and contrast (pneumocologram, barium enema) radiography, ultrasound, and computed tomography were offered. However, after 3 days of no treatment response, the owner elected to proceed with surgical intervention rather than pursue further diagnostic testing because of financial constraints.

The patient was sedated with midazolam 1 mg/kg, intramuscularly (West-ward Pharmaceuticals, Eatontown, NJ USA) and buprenorphine 0.02 mg/kg, intramuscularly, anesthetized with isoflurane via mask induction (3% isoflurane, 3 L/minute oxygen), maintained on mask anesthesia (1.5% to 2.5% isoflurane, 3 L/minute oxygen), and subcutaneously administered 10 mL of LRS. A standard ventral midline celiotomy was performed and intra-abdominal evaluation revealed a 5-cm colonic mass beginning in the transverse colon and extending to the terminal colon (Fig. 2A). The colon, proximal to the mass, was severely distended, although the distal colon appeared healthy. Two aberrant vessels from the right ovarian vasculature to the colonic mass were identified and ligated with 4-0 polydioxanone (PDS) (Ethicon, Johnson & Johnson, Somerville, NJ USA) (Fig. 2B). A colonic resection and anastomosis was performed allowing 1 cm grossly normal margins proximal and distal to the mass. Surgical margins were identified by both

TABLE. Relevant Blood Count and Plasma Biochemistry Values for a Rat (*Rattus norvegicus*) Before Colonic Resection and Anastomosis for Colonic Adenocarcinoma

	Patient	Reference Intervals[27]	Units
Hematocrit	40	38.5 to 49.2	%
White blood cell count	18.7	0.96 to 7.88	$\times 10^3$/UL
Monocytes	4	1.0 to 3.6	%
Total protein	8.7	5.7 to 8.3	g/dL
Albumin	3.3	2.8 to 5.3	g/dL
Alkaline phosphatase	207	18 to 62	mg/dL
Aspartate aminotransferase	159	64 to 222	U/L
Alanine aminotransferase	24	14 to 64	U/L

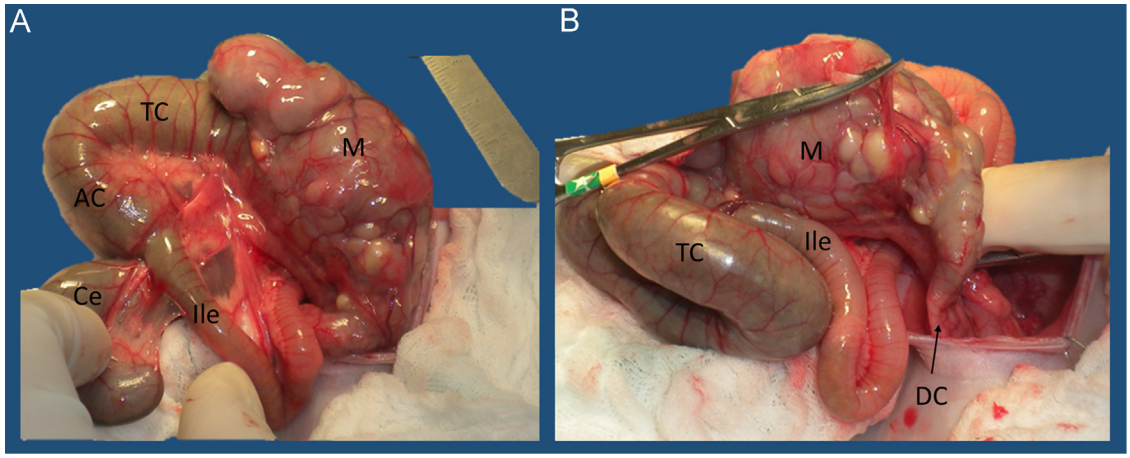

FIGURE 2. Colonic adenocarcinoma of a rat (*Rattus norvegicus*) exteriorized before resection and colocolic anastomosis. (A) Junction of the ileum (Ile), cecum (Ce), and ascending colon (AC). The transverse colon (TC) is severely distended orad to the mass (M). (B) The ileum (Ile) and transverse colon (TC) are reflected cranially and 2 vessels have been ligated to fully exteriorize the mass and show the grossly normal appearing tissue of the descending colon (DC) distal to the mass.

visualization and digital palpation of the junction between affected and adjacent grossly normal tissue; the overall length of colon removed was 7 cm. The distal colon was obliquely incised with Metzenbaum scissors at a 45° angle to accommodate anastomosis with the distended proximal colon. Hemostasis was achieved with radiosurgery and 4-0 PDS. The anastomosis was completed with 5-0 PDS (Ethicon, Johnson & Johnson, Somerville, NJ USA) in 2 hemicircumferential simple continuous patterns. The anastomosis site was "leak tested" by filling the colonic lumen with approximately 1 mL sterile saline injected through the antimesenteric side of the distal colon segment using a 27-gauge needle attached to a 1 mL syringe. During the test, the colon, proximal and distal to the anastomotic site, was gently dilated, confirming free fluid flow through the anastomotic site and no colonic incision leakage. The colonic mesentery was closed and secured using 5-0 PDS. The remaining exploratory abdominal examination revealed no abnormal findings. The surgical site was irrigated with warm sterile saline. The linea was closed with 3-0 PDS (Ethicon, Johnson & Johnson, Somerville, NJ USA) in a simple continuous pattern, the subcutaneous tissues were apposed with 5-0 PDS in a simple continuous pattern, and the skin was closed with 5-0 PDS in an intradermal pattern.

Histologically, the mass was consistent with colonic adenocarcinoma extending to the serosal surface. Multiple abscesses with intralesional bacteria were present in the surrounding tissue. Small, noncontiguous foci of similar neoplastic cells were present in the mucosa adjacent to the surgical margin, but lymphatic or vascular invasion was not observed.

The rat did well following surgery with continued therapy of lactulose, subcutaneous LRS, and syringe feeding. Analgesia was accomplished initially with buprenorphine 0.02 mg/kg, subcutaneously every 12 hours and meloxicam 0.1 mg/kg, subcutaneously every 24 hours (Boehringer-Ingelheim, Ridgefield, CT USA) while hospitalized; tramadol 5 mg/kg, orally every 12 hours for 5 days (Amneal Pharmaceuticals LLC, Bridgewater, NJ USA) and meloxicam 0.1 mg/kg, orally every 24 hours for 3 days were administered following discharge from the hospital. Diarrhea was first noted the evening after the surgical procedure and continued through the following week. However, the patient's feces were soft and formed when reexamined 10 days postsurgery. Lactulose was continued and tapered over 1 week beginning 14 days postsurgery; during this time the feces became more formed and remained normal thereafter. Other than the previously described soft feces, no postoperative gastrointestinal complications were noted. Routine ovariohysterectomy was performed at another veterinary hospital 5 months following the tumor excision with no evidence of disease being noted at the anastomosis site. The rat lived 2 years following colonic resection and was euthanized for issues unrelated to colonic neoplasia.

Postmortem evaluation revealed multiple mammary masses throughout the ventral subcutis with multifocal ulceration of the epidermis and presumptive infiltration into the cranial mediastinum and adjacent musculature. Within

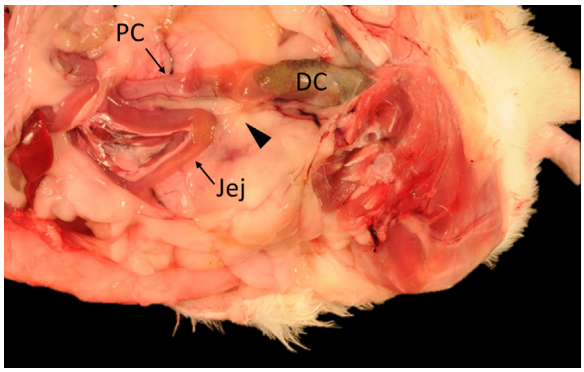

FIGURE 3. Postmortem evaluation of a rat (*Rattus norvegicus*) 2 years after resection of colonic adenocarcinoma and colocolic anastomosis. Intraperitoneal adhesions (black arrow head) can be identified between the jejunum (Jej) and colon at the anastomotic site, which was the junction between the proximal colon (PC) and descending colon (DC).

the abdomen, the most significant gross lesion noted was a focal fibrous adhesion between the colon and dorsal body wall and between the mesentery and a loop of jejunum (Fig. 3). The adhesion expanded and slightly compressed the left ureter, resulting in mild left hydroureter and hydronephrosis. There was no gross evidence of regrowth of a colonic neoplasm (Fig. 4). Histologic examination of the mammary masses confirmed infiltration into the cranial mediastinum and skeletal muscle. Based on regional cellular pleomorphism and infiltrative behavior, these masses were diagnosed as mammary fibrosarcomas arising within a fibroadenoma. There was no histologic evidence of regrowth or metastasis of the excised colonic adenocarcinoma; the surgical site was confirmed by the presence of 2 pieces of remnant suture observed amidst fibroblasts and macrophages along the serosal surface.

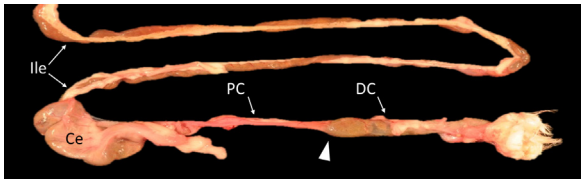

FIGURE 4. The distal portion of the intestinal tract from a rat (*Rattus norvegicus*) 2 years following resection of colonic adenocarcinoma and colocolic anastomosis. The anastomotic site is indicated by the white arrow head. The colon is labeled as proximal colon (PC) and descending colon (DC) owing to previous removal of 7 cm of colon resulting in ill-defined margins of the ascending and transverse colon. Ileum (Ile) and cecum (Ce) appear unaffected.

DISCUSSION

This case describes successful surgical management of a large colonic adenocarcinoma leading to clinical obstipation in a rat. Few cases of naturally occurring colonic adenocarcinoma are reported in rats, which suggests rarity of the tumor type in this species. Experimentally, chemically induced colonic neoplasia in rats has been used as a model for human intestinal adenocarcinoma to evaluate novel chemoprevention compounds.[1-5] In general, alimentary neoplasia is uncommon in companion animals, comprising $<1\%$ of submissions in various reports.[6-8] Lymphoma comprises approximately 30% and 6% of all feline and canine alimentary tumors, respectively, with adenocarcinoma being the second most frequent gastrointestinal neoplasm diagnosed in both species.[9,10] Jejunal adenocarcinoma is more common in felines, whereas colorectal adenocarcinoma is more common in dogs.[7,8] Additionally, colonic adenocarcinoma has been reported in a Rhesus macaque, horse, leopard gecko, and a group of captive Amur rat snakes.[11-14]

No pathognomonic clinical signs of colonic adenocarcinoma in rats have been established, although the rat in this case was obstipated with radiographic evidence of dilated bowel and a midabdominal mass effect. The hematologic findings of leukocytosis with a relative monocytosis were consistent with physiologic stress and chronic inflammation, possibly related to the peritumoral abscesses.[15] Elevated alkaline phosphatase may be owing to the physiologic stress of gastrointestinal dilation, although hepatopathy or other pathology could not be ruled out without further diagnostics.[16]

Although radiographic images failed to show a discrete mass, the presence of marked bowel and abdominal distention elevated the clinical probability of a tissue mass. Therefore, without clinical improvement following 3 days of medical management, surgical intervention was elected. Pre-surgical evaluation by compression radiography using a wooden paddle or other compression tool to displace the ingesta may have helped to isolate a discrete mass, but was not completed because of financial constraints and high suspicion of either colonic impaction or mass requiring imminent surgical intervention regardless of the findings.[17] Abdominal ultrasonographic evaluation may have identified a discrete mass or revealed its specific location similar to that reported in a rabbit with jejunal adenocarcinoma.[18] Other important information

that may have been provided by ultrasonographic evaluation includes local involvement with adjacent structures, confirmation of colonic lumen occlusion, and vascularity to the tumor; however, this procedure was not performed owing to owner financial constraints. Similarly, positive contrast intraoperative ultrasound may have helped delineate irregular tissue from healthy colonic tissue to aid in identifying the sections of colon that needed to be resected; however, this modality was not available at the institution in which the surgical procedure was performed.[19] Although the surgical biopsy was not able to confirm tumor free margins, complete removal was evidenced by lack of tumor regrowth 2 years following excision of the mass.

The surgical procedure completed in the rat described in this report is similar to that previously described for rats as a left hemicolectomy that includes the removal of the transverse and distal colon.[20] A right hemicolectomy and subtotal colectomy were also described in the same report, although each of these procedures included removal of the cecum. The cecum and ascending colon were spared in this rat, which is consistent with what has been described in dogs and cats as a subtotal colectomy with colocolic anastomosis.[21]

Colorectal anastomotic leakage is the most important complication of colorectal surgery in humans, accounting for one-third of postoperative deaths.[22] In a study evaluating anastomoses and insufficient suturing, rat colonic anastomoses with 5 interrupted sutures had a significantly higher incidence of leakage than anastomoses with 12 simple interrupted sutures 7 days following the surgical procedure.[22] The actual anastomosis in this case report was completed with 2 hemicircumferential simple continuous sutures, each beginning at the mesenteric side and extending around the colon in opposite directions to meet at the anti-mesenteric side, and resulted in no anastomotic leakage.

The formation of fibrous adhesions following abdominal surgery is widely considered a risk of abdominal surgery and was reported to cause severe morbidity in other species, such as rabbits.[23] Studies using the rat model for prevention of postoperative intraperitoneal adhesions examined intraperitoneal administration of various compounds.[24-27] In this case, antiadhesion compounds were not used and it is not known which surgery (colonic resection or ovariohysterectomy) led to adhesion formation, although no adhesions were noted 5 months after the colonic resection. The fibrous connective tissue that surrounded the left ureter likely contributed to increased ureteral pressure, resulting in the mild subclinical hydroureter and hydronephrosis seen in this case.

This article exemplifies that neoplastic disease (e.g., colonic adenocarcinoma) resulting in obstipation is not necessarily a fatal event when treated with surgical resection. Two years after the colonic resection and anastomosis, there was no gross or histologic evidence of regrowth or metastasis. Surgical intervention, in lieu of medical management alone or euthanasia, may be a successful treatment option for rats that exhibit either a partial obstruction or overt obstipation secondary to gastrointestinal neoplasia.

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