

Case Report

Spontaneous Gastric Carcinomas in Sooty Mangabeys (*Cercocebus atys*)

Prachi Sharma,^{1*} Joyce K Cohen,^{2,4} Katherine S Paul,^{2,4} Cynthia L Courtney,^{1,5} Zachary P Johnson,³ and Daniel C Anderson¹

Sooty mangabeys (*Cercocebus atys*) are native to West Africa and are a natural host of SIV, which is implicated in the origin of HIV2. They have been used in studies of AIDS pathogenesis, leprosy, immune responses, reproductive biology, and behavior. Spontaneous tumors have rarely been reported in this species. However, we noted spontaneous gastric carcinomas in 8 sooty mangabeys. Four male and 4 female mangabeys had mild to severe chronic weight loss, with abdominal distention in 5 of 8 animals. At necropsy, 7 of the 8 mangabeys had prominent large ulcerated masses with severe, diffuse thickening of the pyloric wall at or near the gastric–duodenal junction, which often partially occluded the gastric lumen. Early carcinoma was an incidental finding in one mangabey. Histologically, all of the tumors were classified as adenocarcinomas. Adenocarcinomas were noncircumscribed with infiltrates of neoplastic epithelial cells, often arranged in acini. In 3 mangabeys, these infiltrates were transmural and invaded surrounding tissue locally. The adenocarcinomas were locally invasive, with metastasis to regional lymph nodes in 2 animals, but widespread metastasis was not seen. Anisocytosis, anisokaryosis, and high mitotic rates were seen in all 8 tumors. In the samples available, serology and Steiner stain did not detect *Helicobacter*, and immunohistochemistry failed to reveal *Helicobacter* or Epstein–Barr virus, 2 potential causes for human gastric carcinomas.

Gastric carcinoma is the fourth most common cancer in the world, second to lung cancer in mortality, with as many as 700,000 deaths annually in humans.¹⁰ An increased risk of gastric cancer has been associated with colonization of the stomach wall with *H. pylori*,²⁶ exposure to dietary carcinogens (for example, nitrosamines in smoked fish and pickled vegetables),³⁴ and genetic predisposition.^{22,24} An increased incidence of intestinal metaplasia preceded by gastric inflammation has been seen in populations at high risk for gastric cancer, suggesting a role for environmental factors.¹⁵ More men than women have been diagnosed with gastric carcinoma, for which estrogen has been considered to be protective.⁶ Gastric carcinomas are generally uncommon in domestic animals, but this tumor is the most common adenocarcinoma in dogs, predominantly in male dogs, with more than half of the lesions reported occurring in the pyloric region.⁹ Rare cases in cats and cattle have also been described.⁹

Nonhuman primates have been used as animal models for experimental induction of gastric carcinogenesis with or without *H. pylori* infection.^{20,25} The Japanese macaque (*Macaca fuscata*) has been found to be a valuable model to study the potential role of *H. pylori* infection in the pathogenesis of gastric carcinoma.¹⁸ Rhesus macaques (*Macaca mulatta*) have been used to examine the role of an oral carcinogen (similar to the nitrosamines found in

pickled vegetables) and *H. pylori* infection in synergistically inducing gastric neoplasia.²⁰ In rhesus and crab-eating (*Macaca irus*) macaques, chemically induced, poorly differentiated, and signet-ring–cell carcinomas, have been documented more often than have moderately or well-differentiated gastric carcinomas.²⁵ Other than the reports of experimentally induced gastric carcinomas, spontaneous gastric carcinomas are uncommon in nonhuman primates. Rare cases have been reported in 2 rhesus macaques, a vervet monkey, and a Barbary ape.^{11,17,21,29,31}

Sooty mangabeys (*Cercocebus atys*), native to West Africa and thought to be a source of HIV2 in nature,^{4,28,30} are used in studies related to AIDS pathogenesis, reproductive biology, and behavior. This animal species also exhibits particular immune features: it has been a model of human lepromatous leprosy¹⁴ and tends to exhibit a general Th2 skew in immune responses¹ with potent natural killer cell responses,²⁷ which are a control mechanism of neoplasia. Neoplasia has rarely been reported in sooty mangabeys,^{7,23} even though these animals are protected under the US Fish and Wildlife Service and live normal life spans. Here we describe features of spontaneous gastric carcinoma in 8 sooty mangabeys.

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History. Eight (4 male and 4 female) mangabeys were born at the Field Station of the Yerkes National Primate Research Center and were housed in accordance with the *Guide for the Care and Use of Laboratory Animals*¹⁴ and Animal Welfare Act and Regulations.^{2,3} Most had been maintained in social colonies in an indoor–outdoor compound since birth. All colony animals were fed a standard monkey chow diet (Purina LabDiet 5037, St Louis, MO) with daily approved enrichment. Typical clinical presentations

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¹Division of Pathology, ²Division of Animal Resources, and ³Division of Cognitive and Developmental Neuroscience, Yerkes National Primate Research Center, ⁴Division of Psychiatry and Behavioral Sciences and ⁵Department of Pathology and Laboratory Medicine, School of Medicine, Emory University, Atlanta, Georgia.

*Current affiliation: Division of Scientific Resources, NCEZID, Centers for Disease Control, Atlanta, Georgia.

Corresponding author. Email: psharm9@emory.edu

Animal no.	Signalment	Clinical history	Viral status		Gross lesions
			SIV	STLV	
1	Male, 11 y 5 mo	Pale mucus membranes, hypoalbuminemia, anemia, abdominal mass palpable under the right rib cage. Radiographs suggested distended stomach. Euthanized 9 d later.	+	-	Ulcerated mass in the pylorus of stomach (6.0 × 4.5 × 3.5 cm). Thickened gastric wall. Grayish, irregular streaks on the serosal surface.
2	Male, 14 y 9 mo	Diabetic. Markedly distended stomach; relieved by stomach tube. Found recumbent in his cage 4 d later. Dehydrated and hypoglycemic. Stomach distended with fluid and ingesta mixed with gas. The animal died during the night.	-	-	Focal extensive mucosal necrosis and ulceration (6 × 2 cm). Severe focal thickening (0.75 to 1 cm) of pyloric wall and partial lumen occlusion. Extensive adhesion of the gastric serosa with hepatic capsule and mesentery. Hepatomegaly.
3	Male, 12 y	Abdominal distension, weight loss, and bloody diarrhea reported 6 d before the animal was euthanized.	-	-	The gastric pylorus had severe diffuse thickening of the wall (1 cm thick). Ulcerated and hemorrhagic mucosa (5 × 4 cm). Partially occluded lumen.
4	Male, 12 y 5 mo	Marked weight loss. Found recumbent, comatose, hypothermic, and pale, with markedly distended upper abdomen. Small amount of gastric contents removed by nasogastric tube appeared bloody. Euthanized due to poor prognosis.	-	-	The pyloric wall was severely thickened constricting the gastric lumen. The gastric mucosa was focally ulcerated and hemorrhagic.
5	Female, 10 y	Weight loss, severe anemia, hypoproteinemia, hypoalbuminemia, with elevated liver enzymes. Euthanized.	-	-	A large irregular ulcer (approximately 5.0 × 6.0 cm) with deeply umbilicated edges extending from the esophageal junction to the pylorus.
6	Female, 21 y 5 mo	Diabetes with associated weight loss; spondyloarthropathy. Euthanized.	+	+	The mucosa had a focal 2.0-cm-long erosion along with moderate thickening of the gastric wall.
7	Female, 16 y	Weight loss, lethargy, dehydration, hepatomegaly, azotemia, hypoalbuminemia, and elevated liver enzymes. Gastric distension detected on radiographs. The animal was treated with supportive care but continued to deteriorate clinically. Due to a poor prognosis, the animal was euthanized.	+	+	Stomach dilated and enlarged to approximately 5 times normal size. The pyloric region was thickened and ulcerated. The gastric mass appeared to have infiltrated into duodenum and pancreas.
8	Female, 17 y	Weight loss, lethargy, abdominal pain. Euthanized.	+	+	Distended stomach, thickened pyloric wall, focal extensive mucosal ulceration. Adherence of gastric serosa to surrounding mesentery.

STLV, simian T-cell leukemia virus

Figure 1. A brief summary of the clinical and gross necropsy findings in the 8 mangabeys.

included chronic weight loss, with 3 of the 8 mangabeys having acute gastric distension that could not be relieved with a gastric tube. Figure 1 summarizes the signalment, clinical history, viral status, and gross lesions of these animals. Acute gastric distension was present in 3 of the 8 mangabeys, and in 2 of those 3 cases, radiographs were obtained and revealed a severely distended stomach filled with digesta (Figure 2). Necropsy was performed on all animals after natural death (1 animal died while undergoing treatment) or euthanasia (7 animals).

Gross pathology. The typical presentation included a moderately to severely distended stomach with the gastric wall thickened in all cases but one (mangabey no. 6), with early evidence of carcinoma and superficial ulceration. Masses were located in the pyloric region with extension into the gastric-duodenal junction (Figure 3 A and B) and often partially occluded the lumen.

Central portions of gastric mucosa overlying the masses were ulcerated extensively (Figure 3 A and B). In 4 mangabeys, transmural extension of the tumor resulted in adhesion of the gastric serosa to the omentum, liver, duodenum, adjacent lymph nodes, or pancreas or combinations thereof.

Serology. Serum samples of all 8 mangabeys were assessed for antibodies for SIV and simian T-cell leukemia virus; 3 animals were positive for both viruses, and 1 mangabey was positive for SIV only. The serum samples available from 5 mangabeys (no. 1, 3, 5, 6, and 7) were submitted to the Emory Medical Laboratory at the Emory University Hospital for determining antibody titers for *Helicobacter* spp. All 5 samples tested negative for *Helicobacter*, a known contributing factor of gastric carcinoma in humans.²⁶

Histopathology. Tissue specimens were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 6 µm, and

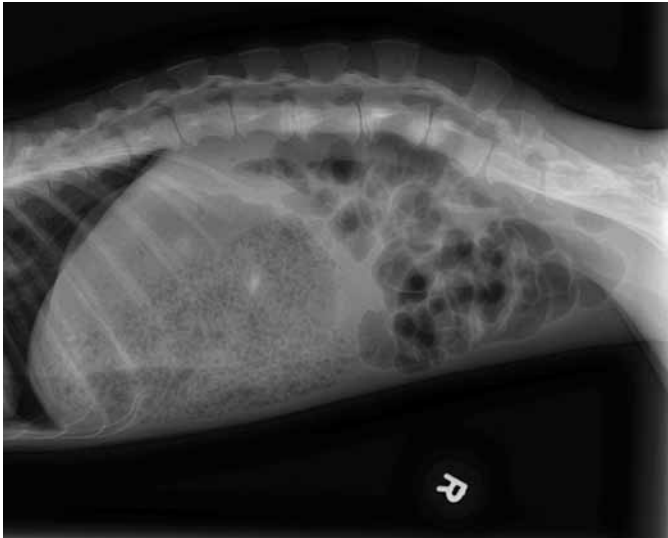


Figure 2. Lateral radiograph of animal 7 showing a severely distended stomach filled with digesta.

stained with hematoxylin and eosin. All 8 mangabeys had similar lesions, with a diagnosis of adenocarcinoma in the stomach (Figure 3 C and D). In the pyloric region, focal extensive ulceration of gastric mucosa was intermixed with noncircumscribed neoplastic infiltrates of epithelial cells often arranged as acini or solid mass of cells. Frequently, neoplastic cells invaded the submucosa and serosa and were surrounded by a desmoplastic response. Individual neoplastic epithelial cells exhibited cellular polymorphism, anisocytosis, and anisokaryosis. Approximately 1 to 2 mitotic figures were present in each 40 \times field. In 2 cases, neoplastic cells infiltrated into the fibroplasia adhered to the liver, pancreas, and mesentery. In 2 cases, the tumor cells metastasized to the regional lymph nodes.

In all 8 animals, neoplastic lesions were not present in the remainder of the gastrointestinal tract. Other lesions included multifocal vacuolar degeneration of hepatocytes (lipid) with pancreatic islet amyloidosis in the diabetic mangabeys (nos. 2 and 6). Steiner silver staining and immunohistochemistry for *Helicobacter* spp. failed to reveal the bacteria in the gastric masses of mangabeys 1, 2, 3, 4, 5, and 7. Because Epstein–Barr virus has been linked to gastric carcinoma in humans^{5,32} and the virus has been detected by PCR in samples from sooty mangabeys,¹² we tested the gastric masses (animals 1, 2, 3, 4, 5, and 7) for Epstein–Barr virus by immunohistochemistry. None of the specimens showed virus-positive staining.

Discussion

Here we report an unusually high frequency of spontaneous gastric carcinomas in sooty mangabeys, with 8 cases observed since the initial case was identified (approximately a 9-y period). This incidence in mangabeys 10 y of age or younger during the period of this study (total, 106 mangabey necropsies: 67 female and 39 male) in this age range is very high (7.5%), particularly compared with the extremely rare documentation of gastric tumors in rhesus macaques,^{17,29} a commonly used laboratory animal. Our mangabeys ranged in age from 10 to 30 y (median age, 15 y), and unlike the reports of an increased incidence of this tumor in men⁶ and in male dogs,⁹ male and female mangabeys

were affected equally. Typical clinical presentation included moderate to severe chronic weight loss, and 4 of the 8 animals had acute gastric distension which was identified clinically but was unresponsive to treatment. Similar to the reports of this disease in dogs,⁹ the tumor was located in the pylorus of the mangabeys, with thickening of the pyloric wall involving the tumor sites. The gross appearance of the tumor varied from a small, focal mucosal ulceration in a single mangabey to large, locally invasive ulcerated masses (8 animals). The thickened gastric wall frequently resulted in partial occlusion of the gastric–duodenal junction and likely was the reason for the antemortem gastric distension seen in these animals. Histologically, all the tumors were classified as adenocarcinomas, and transmural infiltrates of neoplastic cells were observed in 7 of 8 mangabeys. Peritonitis with adhesions between the gastric serosa, pancreas, mesenteric tissue, and liver resulted from the neoplastic invasion into surrounding tissues in 3 of 8 animals. Metastasis to local abdominal lymph nodes was seen in 2 mangabeys. Widespread tumor dissemination was not observed in any animal.

H. pylori has been linked to an increased incidence of gastric adenocarcinoma in humans.¹⁰ Serum samples were available from 5 of the animals with gastric adenocarcinomas (nos. 1, 3, 5, 6, and 7) for measuring *Helicobacter* titers. All 5 samples tested negative. In addition, immunohistochemistry and Steiner silver staining did not detect the presence of *H. pylori* in the gastric tumors available from 7 animals (no. 1, 2, 3, 4, 5, and 7). Three animals were serologically positive for both SIV and simian T-cell leukemia virus, and one animal was positive for only SIV; these data are consistent with those for other age-matched mangabeys at our facility. Mangabeys are natural hosts of SIV infection and rarely develop immunosuppression²⁸ or signs of disease associated with SIV infection in experimentally infected macaques.¹⁹ Lesions associated with SIV infection were not seen in our 8 mangabeys. Two mangabeys (nos. 2 and 6) with gastric carcinoma also had diabetes, and mangabey 6 was euthanized due to diabetes associated with weight loss; early carcinoma was an incidental finding in this animal. However, clinical diabetes occurs in the same age group and is seen more commonly than gastric carcinomas in aging mangabeys in our colony.⁸

Although gastrointestinal adenocarcinomas, especially colonic adenocarcinomas have frequently been reported to occur in rhesus macaques,³³ to our knowledge there are only 3 previous reports of tumors in sooty mangabeys, consisting of hepatoma,⁷ lymphoma,¹⁹ and squamous cell carcinoma.²³ The current study is the first report of spontaneous gastric carcinoma in this species. Reports in the literature likely are scant due to overall low numbers of captive mangabeys, which generally are kept in small colonies. In contrast, our colony currently houses 176 mangabeys, affording a unique opportunity to further study natural pathology in this species. Furthermore, our colony, established in 1968 from 22 animals, is an aging colony with a high degree of inter-relatedness due to a profound founder effect. Therefore, as the colony ages, we expect to see an increased incidence of neoplasia and, because of inbreeding, these findings may be more representative of our population than sooty mangabeys overall. Tumors of any kind were seen infrequently in our colony until the past decade, with gastric carcinoma first seen in 2002. This pattern may reflect to several factors, in particular, the fact that the colony is aging. Of the 122 mangabeys that died between May 2002 and

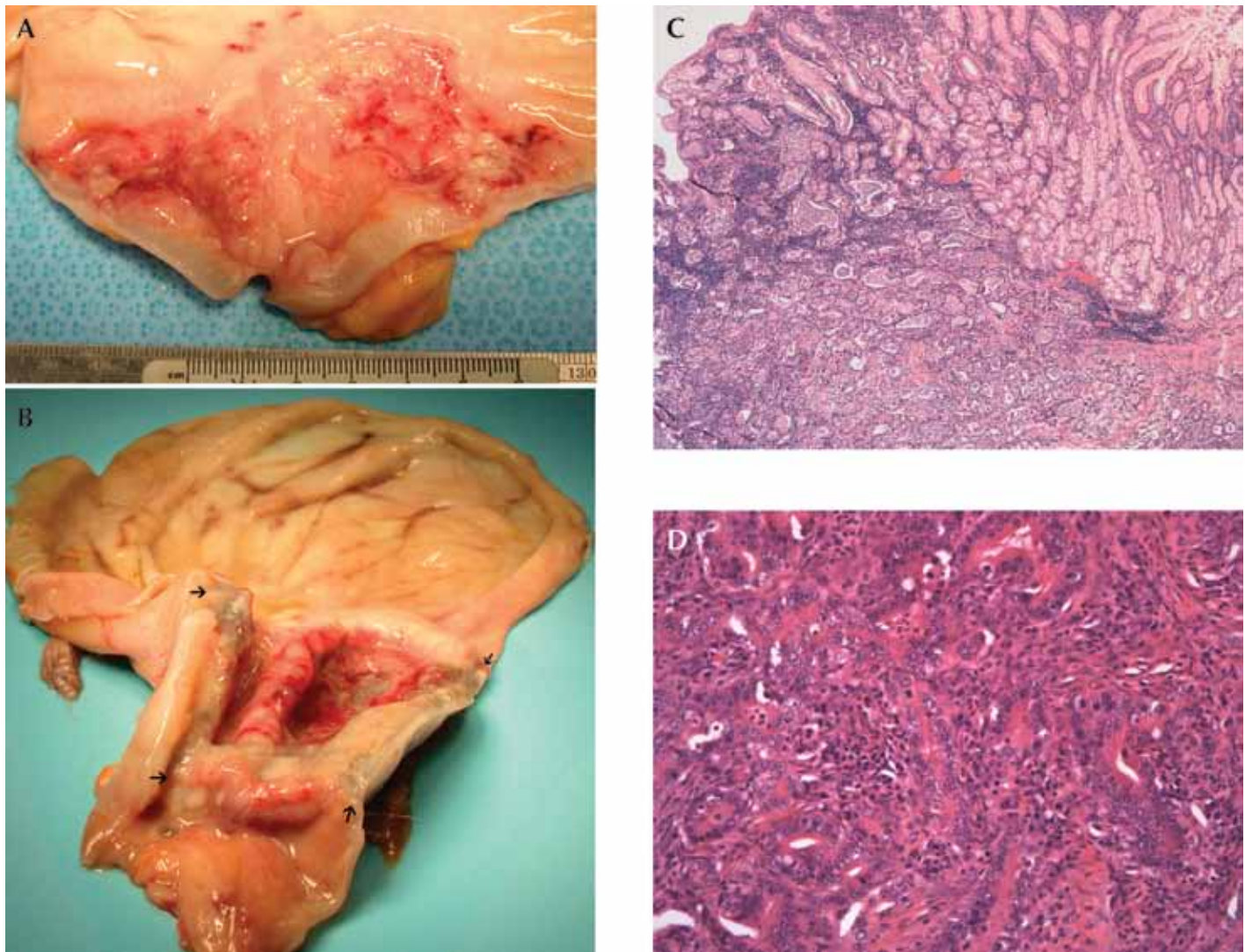


Figure 3. Gross findings. Severely thickened gastric wall with the ulcerated mass in the mucosa of animals (A) 3 and (B) 4. Arrows in panel B show the approximate boundaries of the tumor. Histopathology. (C) Animal 7, mucosal infiltrates of neoplastic cells. Neoplastic cells arranged in acini in animals (C) 7 and (D) 1. Hematoxylin and eosin stain; magnification, $\times 200$ (C), $\times 400$ (D).

December 2010 (the time frame of this study), 106 (86.9%) were at least 10 y old (range, 10 to 32 y).

Because we did not detect evidence of *Helicobacter* in these monkeys, we believe that other environmental or genetic factors may be involved. However, chronic gastritis is a common finding in colony-housed mangabeys, similar to that seen in other commonly housed research animals (for example, rhesus macaques).¹³ Although chronic gastritis is a common condition, its etiology in mangabeys is unknown and should be addressed in future research. *Helicobacter* is a common cause of gastritis in humans and may still be implicated in the disease in mangabeys, but all 7 cases we tested were negative by both silver staining and immunohistochemistry.

In the current study, the incidence of gastric carcinomas in mangabeys at least 10 y old was high, especially when compared with the frequency of the disease in rhesus macaques, in which large intestinal carcinomas are identified more frequently.³³ The paucity of naturally occurring gastric carcinomas in nonhuman

primates suggests that the finding of such neoplasms in sooty mangabeys is therefore unique. Additional studies examining the familial link (if any) between these animals and environmental factors are ongoing to better understand the pathogenesis of gastric carcinoma as well as other disease patterns in our colony.

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