Comparative Medicine
Copyright 2013
by the American Association for Laboratory Animal Science

Vol 63, No 4
August 2013
Pages 361–366

Case Report

Adenocarcinoma of the Ileocolic Junction and Multifocal Hepatic Sarcomas in an Aged Rhesus Macaque (*Macaca mulatta*)

Cynthia D Lang,[1,*] Judith S Daviau,[1] Daniel A Merton,[2] and Susan M Caraker[3]

An aged male rhesus macaque in our colony had decreased appetite and a loss of interest in behavioral testing. CBC analysis revealed a regenerative, microcytic, hypochromic anemia with thrombocytosis, consistent with iron deficiency. A fecal occult blood test was positive. Ultrasound imaging revealed numerous, vascularized focal liver lesions that suggested metastases. The macaque's appetite continued to decrease, and he became more lethargic. At this point, the investigator elected to euthanize the macaque. At necropsy, the ileocolic junction was white and abnormally thickened, and the liver was pale tan with approximately 18 discrete white masses randomly scattered throughout the hepatic parenchyma. Histologically, the mass at the ileocolic junction was identified as an intestinal adenocarcinoma, whereas the liver masses were confirmed to be undifferentiated hepatic sarcomas. This case report describes a rhesus macaque that had 2 unrelated primary neoplasms. A review of the literature indicates that this rhesus macaque is the first reported to have an adenocarcinoma of the ileocolic junction and multiple hepatic sarcomas simultaneously.

Rhesus macaques (*Macaca mulatta*) are genetically similar to humans, have a similar aging phenotype at approximately 3 times the rate of those in humans, and develop spontaneous cancers similar to those in humans.[36] In humans, gastrointestinal carcinomas are relatively common, but most of these lesions arise in the colon and rectum with only a small percentage in the small intestine and ileum.[4,12,15,18] Although the ileocolic junction is considered a common site for intestinal adenocarcinomas in aged rhesus macaques, this tumor has also been found in the duodenum, jejunum, distal ileum, cecum, and colon.[6,13,21-23,25,39] Intestinal adenocarcinomas also occur in aged cynomologus macaques (*Macaca fasicularis*),[39] cotton-top marmosets (*Saguinus oedipus*),[6,10] common marmosets (*Callithrix jacchus*),[6,27] and a squirrel monkey (*Saimiri sciureus*).[24] Cotton-top marmosets often develop adenocarcinomas of the colon, including the cecum–colon, and rectum.[6,10] Common marmosets have been reported to develop adenocarcinomas of the small intestine.[6,27] Adenocarcinoma of the cecum in a squirrel monkey has been reported.[24]

Spontaneous hepatic tumors unrelated to carcinogenic factors, such as aflatoxin B1,[33] occur only rarely in nonhuman primates. In the United States, primary malignant hepatic tumors in humans are rare, and fewer than 1% are reported to be hepatic sarcomas.[1,16,40] Review of the nonhuman primate literature revealed reports of hepatic cholangiocarcinoma in a 25-y-old male capuchin monkey (*Cebus albifrons*),[7] hepatocellular carcinoma in a 24-y-old male squirrel monkey *(Saimiri boliviensi*s)[5] and in a female squirrel monkey (*Saimiri sciureus*) older than 13 y,[28] and hepatocellular carcinoma and cholangiocarcinoma in an African green monkey (*Cercopithecus aethiops*).[34] Spontaneous hepatocellular carcinomas were reported to occur in 2 adolescent male cynomologus macaques younger than 5 y.[31] Hepatic hemangiosarcoma was diagnosed in 3-y-old female rhesus macaque,[26] and hepatic cholangiocarcinoma was found in a rhesus macaque that also had an intestinal adenocarcinoma.[39]

The aged male rhesus macaque (*Macaca mulatta*) in the current case study was found to have adenocarcinoma of the ileocolic junction and multiple, random, discrete neoplasms in the liver, which were identified as undifferentiated sarcomas. No metastases from the intestinal adenocarcinoma were detected, but neoplastic cells similar to those of the undifferentiated hepatic cells were identified in an intestinal artery. The frequency of multiple tumor types in aged nonhuman primates is relevant to the use of older animals in research.

Case Report

This male rhesus macaque was approximately 23.7 y old at presentation. He was born at the California National Primate Research Center, arrived at our facility in October 2008, and was placed on an IACUC-approved Parkinsonian research protocol that included behavioral testing at our AAALAC-accredited facility. The macaque was individually housed in a stainless-steel cage in a room with other rhesus macaques and managed consistent with the regulations of the Animal Welfare Act,[2] Animal Welfare Regulations,[3] and Public Health Service Policy on Humane Care and Use of Laboratory Animals[29] in accordance with standards published in the *Guide for the Care and Use of Laboratory Animals*.[20] The room was environmentally controlled, with a temperature of 21 °C, humidity 45% to 50%; and a 12:12-h, light:dark photoperiod.

Received: 10 May 2012. Revision requested: 11 Jun 2012. Accepted: 22 Jan 2013.
[1]Laboratory Animal Services and [2]The Department of Radiology, Thomas Jefferson University, Philadelphia, Pennsylvania; [3]IDEXX RADIL, Columbia, Missouri.
**Corresponding author: Email: cynthia.lang@jefferson.edu*

The macaque was fed a commercial monkey chow (Lab Diet 5045, PMI Nutrition International, Brentwood, MO) and supplemented with fresh fruits, vegetables, and other enrichment items several times weekly. He received a daily chewable multivitamin containing 18 mg of iron (Centrum Kids Complete, Wyeth Consumer Healthcare, Madison, NJ). At the time of his arrival, he was apparently healthy. He had a hypertrophied frenulum that caused his tongue to protrude forward but it did not cause any physical impairment. Previous records indicated that this macaque had undergone dental work, including extractions and pulpotomies, on multiple occasions, but the previous research history was unknown.

In April 2011, the macaque began to lose weight gradually and had become uninterested in behavioral testing and some food items. To facilitate physical examination, the macaque was sedated by using ketamine hydrochloride (4 mg/kg IM; Ketaset, Fort Dodge Animal Health, Fort Dodge, IA) and dexmeditomidine (0.01 mg/kg IM, Dexdomitor, Fort Dodge Animal Health). After completion of a physical exam, dexmeditomidine was reversed by using atipamezole hydrochloride (0.1 mg/kg IM; Antisedan, Fort Dodge Animal Health). Physical exam of the macaque revealed pale mucous membranes, face, and skin. The macaque was thin and had a body condition score of 1.5 (maximum, 5). CBC analyses indicated a regenerative, microcytic, hypochromic iron-deficiency anemia with thrombocytosis. Clinical chemistries revealed extremely elevated creatine phosphokinase values, elevated low-density lipoprotein concentrations, decreased serum iron concentrations, hypoalbuminemia, and hyperphosphatemia. A fecal occult blood test (Hemoccult, Beckman Coulter, Fullerton, CA) was positive. Antibody serologic viral testing was positive for Epstein–Barr virus, simian virus SA11, simian vacuolating virus 40, *Macacine herpesvirus* 1 (B virus), and foamy virus. Supportive care was begun and included supplementing the animal's diet with a larger variety of fruits and vegetables.

Approximately 2 wk later, the macaque was prepared for radiography and ultrasonography after anesthesia was induced by using ketamine hydrochloride (4 mg/kg IM) and dexmeditomidine (0.01 mg/kg IM). Isoflurane (IsoSol, Abbott Laboratories, Chicago, IL) was administered via face mask at a concentration of 0.5% to 1.0%, to provide additional anesthesia. Thoracic radiographs were unremarkable. Abdominal radiographs revealed an enlarged liver, but no masses were visible. Grayscale ultrasound imaging revealed numerous masses in the liver that demonstrated blood flow on color Doppler imaging (Figure 1 A and B). The largest 2 lesions were approximately 16 mm in longest diameter. The so-called 'target' appearance of the focal liver lesions (that is, hypoechoic rim surrounding an echogenic center[30]) raised our concern that metastases were present. At completion of the imaging studies, anesthesia was reversed with atipamezole hydrochloride (0.1 mg/kg).

The macaque was scheduled for an ultrasound-guided biopsy of the liver lesions approximately 7 d later. However, over the interim, his appetite continued to decrease, and he became more lethargic. To make the macaque more comfortable, buprenorphine (0.005 to 0.01 mg/kg IM once or twice daily; Buprenex, Reckitt Benckiser Pharmaceuticals, Richmond, VA) was administered. At this point, the investigator elected to euthanize the macaque. He was sedated with ketamine hydrochloride (10 mg/kg IM) and euthanized with sodium pentobarbital (150 mg/kg IV; Nembutal, Abbott Laboratories, North Chicago, IL).

Pathology

The liver was pale tan and had approximately 18 discrete white masses randomly scattered throughout the hepatic parenchyma. The masses varied in size; the largest was approximately 16 mm in its longest diameter. The ileocolic junction was white and abnormally thickened. The lungs had a fine, diffuse, black-mesh coloration. The other internal organs were unremarkable in appearance.

Samples of lung, heart, stomach, duodenum, small intestine, large intestine, spleen, kidneys, adrenal glands, liver, gall bladder, pancreas, testes, urinary bladder, skeletal muscle, bone marrow, axillary lymph node, mesenteric lymph node, ileocolic junction, and liver masses were collected. Tissue samples were fixed in 10% neutral buffered formalin and sent to an outside commercial laboratory (IDEXX RADIL, Columbia, MO) for processing. After fixation, the tissues were embedded in paraffin blocks, sectioned, and stained with hematoxylin and eosin. Histologically, the ileocolic junction was a tubular schirrhous adenocarcinoma (Figure 2), with loss of the regular architecture of the ileocolic junction due to invasion of the mucosa, submucosa, muscularis mucosa, and tunica muscularis layers, with basophilic neoplastic cells forming tubular structures. Neoplastic tubules were surrounded by dense fibrous connective tissue, which was infiltrated with lymphocytes and newly formed blood vessels. Neoplastic cells lining the tubules were columnar, with abundant basophilic cytoplasm and basal oval to round nuclei with clumped chromatin. Cells were arranged 1 to 4 cell layers thick, with 1 to 4 mitotic figures per field (400× magnification). The mucosa of the ileocolic junction bordering the adenocarcinoma was proliferative with goblet cell hyperplasia.

The liver had multiple unencapsulated expansile masses of pleomorphic, neoplastic round to polygonal cells (Figure 3 A and B) that had abundant basophilic cytoplasm and medium to large bizarre nuclei with numerous nucleoli (Figure 3 C). Many of the neoplastic cells were multinucleated, and mitotic figures were present at 8 to 10 per field (400× magnification). Neoplastic cells were strongly positive when probed with antibodies to vimentin, a surface marker type III intermediate filament protein, indicating the cells were of mesenchymal origin (Figure 4). In addition, 75% to 90% of the tumor cells were immunoreactive for intermediate cytokeratin filament proteins, which are structural components of epithelial cells (Figure 5). Additional immunohistochemical assays performed to further characterize the liver tumor were negative and ruled out primary hepatocellular carcinoma, adenocarcinoma, neuroendocrine tumors, smooth and striated muscle tumors, and endothelial tumors (Table 1). In addition, large polygonal neoplastic cells in the lumen of a large intestinal artery in the area of the adenocarcinoma were similar in morphology to the undifferentiated cells of the liver and were suggestive of a very early aggregate of metastatic cells. Because these cells were not in any additional sections used for immunohistochemical assays, further characterization was impossible. From these data, we concluded that the hepatic masses were not metastases from the intestinal carcinoma but were undifferentiated sarcomas with epithelial differentiation.

Other abnormalities included cardiomyopathy, characterized by multifocal large areas of myocyte loss and fibrosis. Hypertrophied myocytes bordering the areas of fibrosis had large, elongated nuclei, and vaculolated eosinophilic (and sometimes fragmented and pale eosinophilic) striated cytoplasm. The myocytes in these

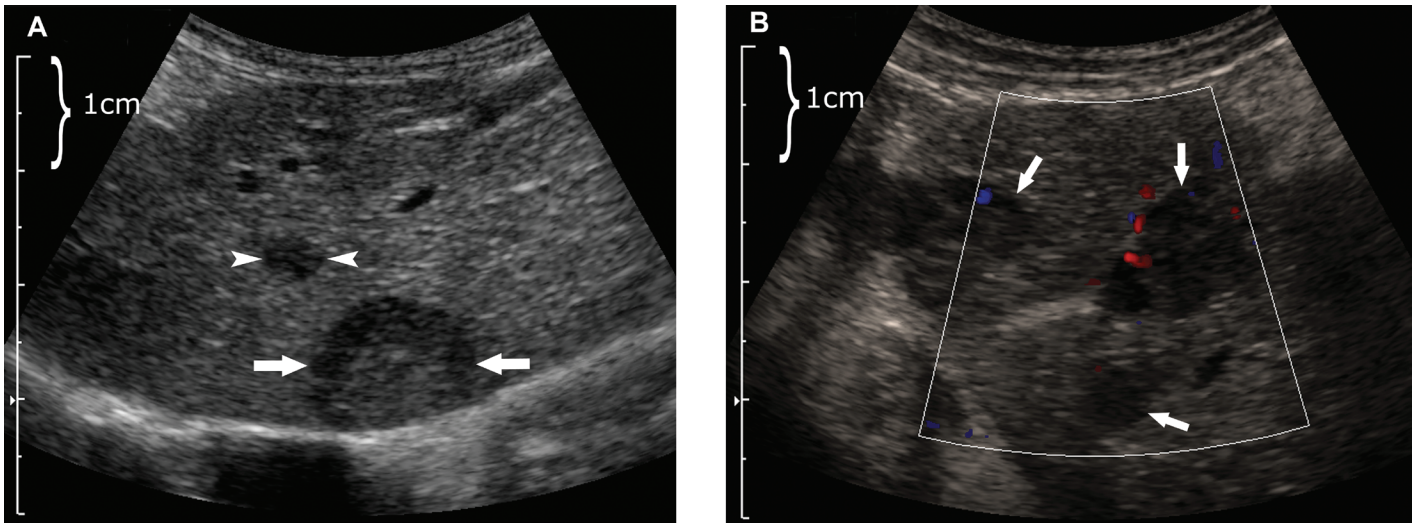

Figure 1. (A) Grayscale ultrasound imaging demonstrates a focal liver lesion (arrows) that measures approximately 16 mm in largest diameter and a smaller lesion (arrowheads) measuring approximately 6 mm. In another view, (B) color Doppler imaging demonstrates vascularity around and within multiple liver lesions (arrows). In this image, red indicates blood flow directed towards the ultrasound transducer whereas blue indicates blood flow directed away from the transducer. These lesions were pathologically proven to represent undifferentiated hepatic sarcomas.

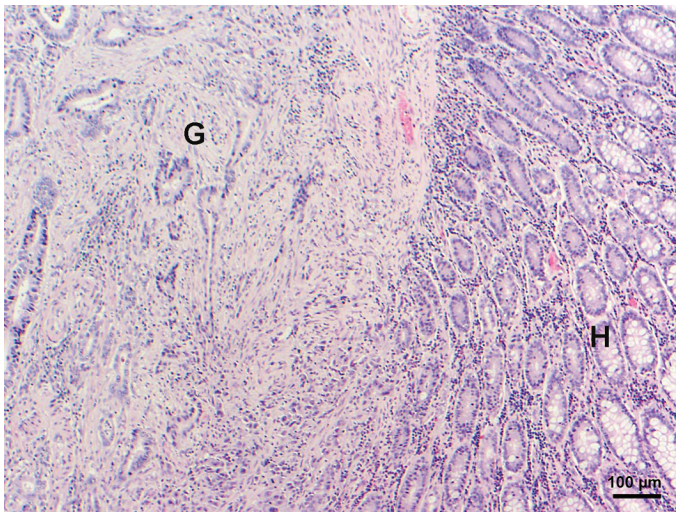

Figure 2. Adenocarcinoma of the ileocolic junction. Hyperplastic mucosa (H) with moderate lymphocytic infiltrate and neoplastic cells forming glands (G) invading the muscularis mucosae. Hematoxylin and eosin stain.

areas were in disarray, with some abnormal myofibrillar branching. The lungs contained multifocal perivascular infiltrates of macrophages with black granular pigment that was birefringent when viewed with polarized light.

Discussion

Intestinal adenocarcinomas in macaques (for example, *Macaca mulatta, Macaca fasicularis*)[6,13,21-23,32,34,35,38,39] are often found in aged geriatric animals but have also been diagnosed in younger animals. When discovered, metastasis primarily involves invasion of regional mesentery lymph nodes[13,24,27,32,35,38,39] but has also been reported to occur in colonic[10,35] and thoracic lymph nodes.[24] Metastases to the liver were found in an aged female rhesus macaque that had a mucinous adenocarcinoma of the ileocecal region[13] and to the regional mesentery lymph nodes, liver, lung, and spleen occurred in a second aged female rhesus macaque that had an adenocarcinoma of the distal ileum.[13] A 13-y-old female rhesus macaque with adenocarcinoma of the ileocecocolic junction had metastases to the mesenteric lymph nodes and the lung,[22] and a 19-y-old female rhesus macaque with adenocarcinoma of the descending colon had hepatic metastases.[22] Over 25 mo at a single institution, 12 female and 1 male rhesus macaques were diagnosed with intestinal adenocarcinoma, 9 of these tumors were located at the ileocecocolic junction, 2 in the small intestine, and 2 in the colon.[32] Of these 13 rhesus macaques, only 1 (a 24-y-old female) had metastases, which affected the peritoneum, liver, kidneys, adrenal glands, diaphragm, and intercostal muscles. A retrospective case review involving 2660 rhesus macaques from the Wisconsin National Primate Research Center and the National Institute on Aging reported that 37% of the primates (average age, 22.2 y) had adenocarcinomas of the colon and ileocecocolic junction, and 5 of those cases had invasion of the regional colonic and mesentery lymph nodes.[35] Another retrospective case review, which described 301 rhesus macaques, reported 4 cases of mucinous adenocarcinoma in the cecum and colon in 13- to 19-y-old animals and 21 cases in 20- to 37-y-olds, with metastases to the ileocecal and mesenteric lymph nodes in 2 cases.[38] A retrospective case review at the California Regional Primate Center included 30 rhesus macaques and 2 cynomologus macaques that had intestinal carcinomas; with the exception of 2 animals that were younger than 12 y, tumors were most prevalent between 13 and 31 y of age (median age, 23.5 y; mean age, 22.1 y); metastases to the regional lymph nodes, liver, lungs, pancreas, and adrenal glands were present.[39]

On occasion, multiple primary tumors have been reported. One group described a 23-y-old female rhesus macaque with 2 primary adenocarcinomas (duodenum and colon),[13] and another[39] reported 4 rhesus macaques with intestinal carcinomas and various unrelated primary tumors, including a squamous cell carcinoma of the cheek pouch, gastric adenocarcinoma, renal adenocarcinoma, and hepatic cholangiocarcinoma.

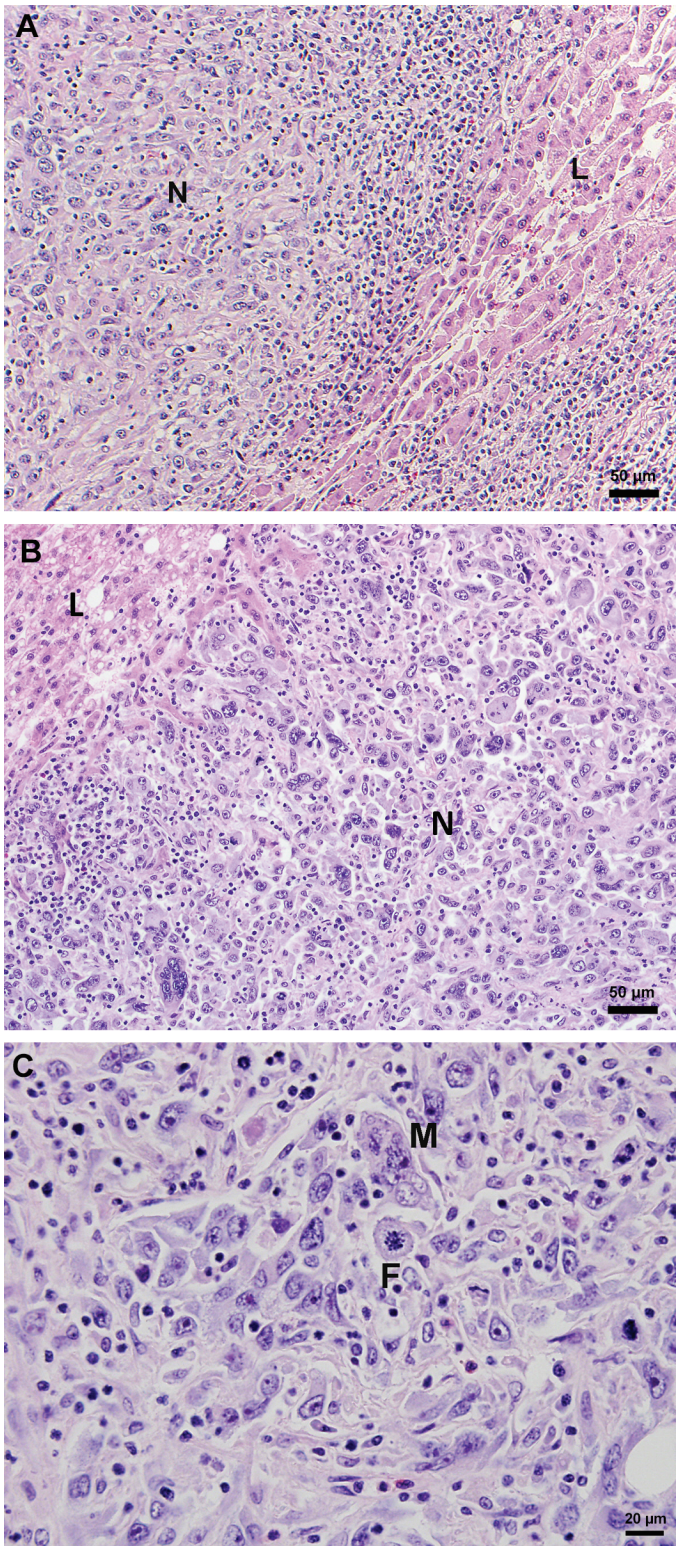

Figure 3. Liver sarcoma. (A and B) Neoplastic cells (N) with lymphocytic infiltrates adjacent to normal liver parenchyma (L). (C) Mitotic figures (F) and large bizarre multinucleated cells (M) of the liver sarcoma.

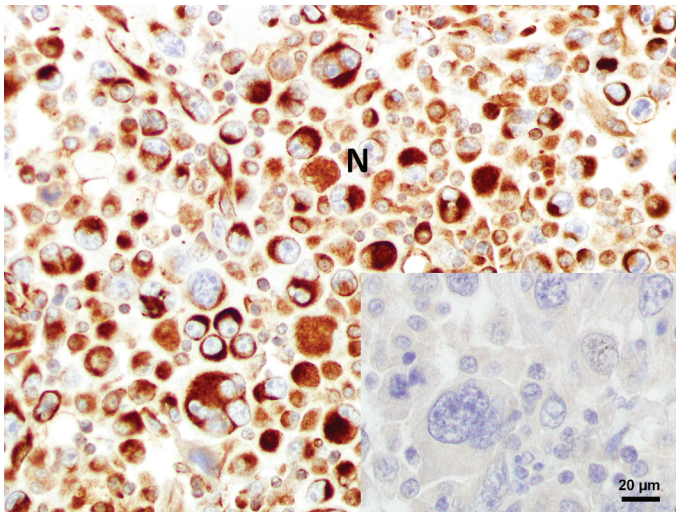

Figure 4. Vimentin immunohistochemical assay of liver sarcoma. Neoplastic cells (N) uniformly labeled with vimentin. N, Neoplastic cells. Inset, Vimentin immunohistochemical assay with negative control antibody.

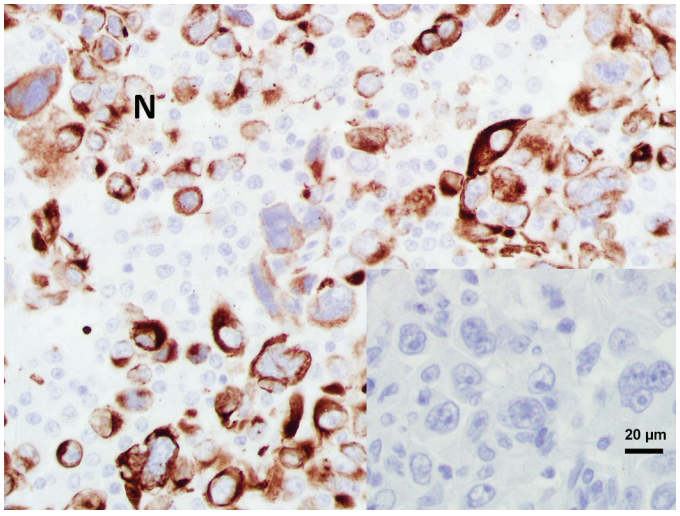

Figure 5. Cytokeratin AE1/AE3 immunohistochemical assay of liver sarcoma. Neoplastic cells labeled with cytokeratin AE1/AE3. N, Neoplastic cells. Inset, cytokeratin AE1/AE3 immunohistochemical assay with negative control antibody.

The macaque we report here was positive for several viruses. Foamy viruses are ubiquitous in adult macaques in the absence of clinical disease.[17] *Macacine herpesvirus* 1 (B virus) and lymphocryptoviruses (closely related to Epstein–Barr virus, *Human herpesvirus* 4) both produce persistent latent infections and are ubiquitous in adult macaque populations, with greater than 90% seropositivity for lymphocryptoviruses[9] and 70% to 100% seropositivity for *Macacine herpesvirus* 1.[14] Reactivation of *Macacine herpesvirus* 1 is usually asymptomatic but can occasionally cause oral herpetic lesions[19] and rarely disseminated disease consisting of inflammation and necrosis.[8,36] In immunocompetent macaques, lymphocryptoviruses infections are normally asymptomatic but can produce atypical lymphocytosis with experimental infections.[9] Immunocompromised macaques infected with lymphocryptovirusus can develop oral hairy leukoplakia, non-

Table 1. Results of immunohistochemical assays used to characterize a hepatic mass in an aged rhesus macaque

Antigen	Specificity/reactivity	Result
Vimentin	Surface marker type III intermediate filament protein is expressed in cells of mesenchymal origin, including fibroblasts, smooth muscle, and endothelium.	4+
Cytokeratin AE1/AE3	Intermediate filament protein, cytokeratin, is expressed in simple and stratified epithelia. Cytokeratins 1–8, 10, 14–16, and 19 are included.	3+
Synaptophysin	Neuronal synaptic vesicle membrane glycoprotein is expressed in neuroendocrine cells and neoplasms.	no reactivity
CD31	Platelet endothelial cell adhesion molecule 1 is expressed on the surface of endothelial cells.	no reactivity
Smooth muscle actin	α smooth muscle actin is expressed in smooth muscle cells, pericytes, myoepithelial cells, and some stromal cells.	no reactivity
Desmin	Type III intermediate filament protein is expressed in striated and smooth muscle cells.	no reactivity
HepPar 1 (hepatocyte)	Antibody to a hepatocyte mitochondrial protein that is reactive to cells of hepatocellular carcinoma.	no reactivity
MOC31	Epithelial surface glycoprotein expressed on most epithelial cells except hepatocytes; used to distinguish metastatic adenocarcinoma from hepatocellular carcinoma or reactive mesothelial cells.	no reactivity

4+, >90% of tumor cells have intense staining; 3+, 75% to 90% of tumor cells have intense staining.

Hodgkin lymphoma, mycosis fungoides-like lymphoma, and B cell lymphoproliferative disorder after organ or bone marrow transplantation.[9] Simian rotavirus strain SA11 rarely causes disease in the natural host; disease when induced in the experimental state manifests as diarrhea.[17] SV40 polyoma virus is indigenous in macaques as well. Concurrent infection with simian type D retrovirus can cause demyelinating CNS disease, known as progressive multifocal leukoencephalopathy.[17] Although we cannot completely rule out the possibility, these viruses were not a likely cause of the intestinal adenocarcinoma or hepatic sarcomas in our macaque.

Kaposi sarcoma is a tumor caused by human herpesvirus 8 and occurs in various organs including the liver.[25,37] Rhadinovirus 1 (retroperitoneal fibrosis-associated herpesvirus) and rhadinovirus 2 (rhesus rhadinovirus) are related to HHV8.[17] Macaques infected with rhesus rhadinovirus alone or coinfected with SIV may develop lymphadenopathy, but concurrent lymphomas and retroperitoneal fibromatosis (a Kaposi-sarcoma-like lesion) have not been reported. Retroperitoneal fibromatosis has been reported to occur in macaques coinfected with simian type D retrovirus 2.[17,41] Serologic assays are unavailable for rhadinovirus 1 and 2.[17,41] Our macaque was seronegative for SIV, and his serologic status for simian retrovirus was unknown. However, the histology of this lesion was not characteristic of retroperitoneal fibromatosis.

In the macaque we present, the animal's pale color on physical exam, CBC results, serum chemistry data, and occult fecal tests all suggested iron-deficiency anemia. One of the primary causes of iron-deficiency anemia is chronic gastrointestinal bleeding associated with neoplasia such as carcinoma, lymphoma, leiomyoma, and leiomyosarcoma.[11] Other conditions that can cause gastrointestinal tract bleeding include gastroduodenal ulceration, which is often associated with vomiting and heavy endoparasite burdens.[11] Our macaque was diagnosed as having an intestinal adenocarcinoma at the ileocolic junction. His abdominal ultrasound imaging combined with his recent clinical presentation (that is, gradual weight loss and loss of appetite) suggested that the multiple masses in the liver were gastrointestinal tract metastases. The liver is a site of distant metastasis, particularly for cancers of the large bowel.[39] However, histology revealed that the liver lesions in our macaque were undifferentiated sarcomas. Because this animal's study history before arriving to our institution was unknown, exposure to hepatic carcinogens cannot be ruled out. Nevertheless, our macaque did not have metastatic tumors in the liver but rather 2 unrelated primary malignancies. In conclusion, this case study appears to be the first published report that describes a nonhuman primate with concurrent primary intestinal adenocarcinoma and hepatic sarcomas.

References

1. **Anderson BB, Ukah F, Tette A, Villaflor S, Koh D, Seton P.** 1992. Primary tumors of the liver. J Natl Med Assoc **84:**129–135.
2. **Animal Welfare Act as Amended.** 2007. 7 USC §2131–2156.
3. **Animal Welfare Regulations.** 2008. 9 CFR § 3.129.
4. **Beart RW, Steele GD, Menck HR, Chmiel JS, Ocwieja KE, Winchester DP.** 1995. Management and survival of patients with adenocarcinoma of the colon and rectum: a national survey of the Commission on Cancer. J Am Coll Surg **181:**225–236.
5. **Borda JT, Ruiz JC, Sánchez-Negrette M.** 1996. Spontaneous hepatocellular carcinoma in *Saimiri boliviensis.* Vet Pathol **33:**724–726.
6. **Brack M.** 1998. Gastrointestinal tumors observed in nonhuman primates at the German Primate Center. J Med Primatol **27:**319–324.
7. **Brown RJ, O'Neill TP, Kessler MJ, Andress D.** 1980. Cholangiocarcinoma in a capuchin monkey (*Cebus albiforns*). Vet Pathol **17:**626–629.
8. **Carlson CS, O'Sullivan MG, Jayo MJ, Anderson DK, Harber ES, Jerome WG, Bullock BC, Heberling RL.** 1997. Fatal disseminated *Cercopithecine herpersvirus* 1 (herpes B) infection in cynomolgus monkeys (*Macaca fascicularis*). Vet Pathol **34:**405–414.
9. **Carville A, Mansfield KG.** 2008. Comparative pathology of macaque lymphocryptoviruses. Comp Med **58:**57–67.
10. **Chalifoux LV, Bronson RT.** 1981. Colonic adenocarcinoma associated with chronic colitis in cotton top marmosets, *Saguinus oedipus.* Gastroenterology **80:**942–946.
11. **Couto CG.** 2003. Anemia, p 1156–1169. In: Nelson RW, Couto CG, editors. Small animal internal medicine. St Louis (MO): Mosby.
12. **Dabaja BS, Suki D, Pro B, Bonnen M, Ajani J.** 2004. Adenocarcinoma of the small bowel. Cancer **101:**518–526.
13. **DePaoli A, McClure HM.** 1982. Gastrointestinal neoplasms in nonhuman primates: a review and report of 11 new cases. Vet Pathol Suppl **7:**104–125.
14. **Elmore D, Elberle R.** 2008. Monkey B virus (*Cercopithecine herpesvirus* 1). Comp Med **58:**11–21.
15. **Farhat MH, Shamseddine AI, Barada KA.** 2008. Small bowel tumors: clinical presentation, prognosis, and outcome in 33 patients in a tertiary care center. J Oncol **2008:**212067.
16. **Forbes A, Portmann B, Johnson P, Williams R.** 1987. Hepatic sarcomas in adults: a review of 25 cases. Gut **28:**668–674.

17. **Gardner MB, Luciw PA.** 2008. Macaque models of human infection disease. ILAR J **49:**220–255.
18. **Hosono S, Ohira M, Maeda K, Muguruma K, Nishihara T, Inoue T, Yashiro M, Hirakawa K.** 2006. Synchronous adenocarcinoma of the ileum and transverse colon detected by capsule endoscopy: report of a case. Surg Today **36:**663–665.
19. **Huff JL, Barry PA.** 2003. B virus (*Cercopithecine herpesvirus* 1) infection in humans and macaques: potential for zoonotic disease. Emerg Infect Dis **9:**246–250.
20. **Institute of Laboratory Animal Research.** 2011. Guide for the care and use of laboratory animals, 8th ed. Washington (DC): National Academies Press.
21. **Johnson EH, Morgenstern SE, Perham JM, Barthold SW.** 1996. Colonic adenocarcinoma in a rhesus macaque (*Macaca mulatta*). J Med Primatol **25:**435–438.
22. **Kerrick GP, Brownstein DG.** 2000. Metastatic large intestinal adenocarcinoma in 2 rhesus macaques (*Macaca mulatta*). Contemp Top Lab Anim Sci **39:**40–42.
23. **Lembo TM, Tinkey PT, Cromeens DM, Gray KN, Price RE.** 1997. Stenosing colonic adenocarcinoma in a female rhesus monkey. J Med Primatol **26:**229–232.
24. **Lenz B.** 1994. Metastasizing adenocarcinoma of the cecum in a squirrel monkey (*Saimiri sciureus*). Vet Pathol **31:**276–278.
25. **Luburich P, Bru C, Ayuso MC, Azón A, Condom E.** 1990. Hepatic Kaposi sarcoma in AIDS: US and CT findings. Radiology **175:**172–174.
26. **Mejia AF, Gierbolini L, Jacob B, Westmoreland SV.** 2009. Pediatric hepatic hemangiosarcoma in a rhesus macaque (*Macaca mulatta*). J Med Primatol **38:**121–124.
27. **Miller AD, Kramer JA, Lin KC, Knight H, Martinot A, Mansfield KG.** 2010. Small intestinal adenocarcinoma in common marmosets (*Callithrix jacchus*). Vet Pathol **47:**969–976.
28. **Morris TH, Abdi MM.** 1996. Hepatocellular carcinoma in a squirrel monkey (*Saimiri sciureus*). J Med Primatol **25:**137–139.
29. **Office of Laboratory Animal Welfare.** 2002. Public health service policy on humane care and use of laboratory animals. Bethesda (MD): National Institutes of Health.
30. **Parkulekar SG, Bree RL.** 1998. Liver, p 642. In: McGahn JP, Goldberg BB, editors. Diagnostic ultrasound: a logical approach. Philadelphia (PA): Lippencott–Raven.
31. **Reindel JF, Walsh KM, Toy KA, Bobrowski WF.** 2000. Spontaneous occurring hepatocellular neoplasia in adolescent cynomolgus monkeys (*Macaca fascicularis*). Vet Pathol **37:**656–662.
32. **Rodriguez NA, Garcia KD, Fortman JD, Hewett TA, Bunte RM, Bennett BT.** 2002. Clinical and histopathological evaluation of 13 cases of adenocarcinoma in aged rhesus macaques (*Macaca mulatta*). J Med Primatol **31:**74–83.
33. **Sieber SM, Correa P, Dalgard DW, Adamson RH.** 1979. Induction of osteogenic sarcomas and tumors of the hepatobiliary system in nonhuman primates with aflatoxin B_1. Cancer Res **39:** 4545–4554.
34. **Seibold HR, Wolf RH.** 1973. Neoplasms and proliferative lesions in 1065 nonhuman primate necropsies. Lab Anim Sci **23:**533–539.
35. **Simmons HA, Mattison JA.** 2011. The incidence of spontaneous neoplasia in 2 populations of captive rhesus macaques (*Macaca mulatta*). Antioxid Redox Signal **14:**221–227.
36. **Simon MA, Daniel MD, Lee-Parritz D, King NW, Ringler DJ.** 1993. Disseminated B virus infection in a cynomologus monkey. Lab Anim Sci **43:**545–550.
37. **Tanaka T, Masuda G, Takechi A, Kobayashi H, Tanaka S, Koike M.** 1995. A case of AIDS-related hepatic Kaposi's sarcoma. J Gastroenterol **30:**268–272.
38. **Uno H, Alsum P, Zimbric ML, Houser WD, Thomson JA, Kemnitz JW.** 1998. Colon cancer in aged captive rhesus monkeys (*Macaca mulatta*). Am J Primatol **44:**19–27.
39. **Valverde CR, Tarara RP, Griffey SM, Roberts JA.** 2000. Spontaneous intestinal adenocarcinoma in geriatric macaques (*Macaca* sp.). Comp Med **50:**540–544.
40. **Weitz J, Klimstra DS, Cymes K, Jarnagin WR, D'Angelica M, La Quaglia, MP, Fong Y, Brennan MF, Blumgart LH, DeMatteo RP.** 2007. Management of primary liver sarcomas. Cancer **109:** 1391–1396.
41. **Westmoreland SV, Mansfield KG.** 2008. Comparative pathobiology of Kaposi sarcoma-associated herpesvirus and related primate rhadinoviruses. Comp Med **58:**31–42.