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Gastrointestinal Stromal Tumors in a Baboon, a Spider Monkey and a Chimpanzee and a Review of the Literature

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Abstract

Background—Gastrointestinal stromal tumors (GISTs) are believed to originate from the intestinal pacemaker cells (interstitial cells of Cajal) or their progenitor cells. Spontaneous tumors have been reported in dogs, horses, rhesus, and a chimpanzee and they have been produced experimentally in mice and rats. GISTs represent a diagnostic challenge because they cannot be differentiated from nonlymphoid mesenchymal tumors without using human c-kit (CD117) immunohistochemistry.

Methods—Three neoplasms were incidental findings at necropsy in the stomachs of a baboon and a spider monkey and in the rectum of a chimpanzee.

Results—The GISTs were initially diagnosed grossly and histologically with hematoxylin and eosin as leiomyomas. Immunohistochemical analysis revealed all three were c-kit (CD117) positive.

Conclusions—These are the first reports of GISTs in the baboon and spider monkey and the second in a chimpanzee. The occurrence of GISTs in nonhuman primates may provide a unique opportunity to study these tumors.

Keywords

Cancer; neoplasm; nonhuman primate; *Papio anubis*; *Ateles paniscus*; *Pan troglodytes*; interstitial cells of Cajal

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms that arise from the wall of the gastrointestinal tract. They are generally small and benign but may be large and malignant. Increasing evidence suggests that GISTs originate from the intestinal pacemaker cells (interstitial cells of Cajal) or their progenitor cells. These cells belong to the autonomic nervous system, which send signals to the gastrointestinal tract (GI), and hence are called the “pacemaker” cells of the GI tract. These mesenchymal tumors can develop throughout the GI tract, including the omentum and mesentery [6]. They are associated with kit or platelet-derived growth factor receptor- α (PDGFRA) signaling driven mechanisms. Kit is a growth factor transmembrane receptor and derived from proto-oncogene c-kit receptor tyrosine kinases. Generally, GISTs express mutant isoforms of kit or PDGFRA. Kit- or PDGFRA-oncoprotein- driven downstream signaling and cytogenetic changes are similar in nature to tumor progression [9,20]. These neoplastic cells are generally positive for the c-kit

proto-oncogene (85%-94%), the CD34 antigen (52%-72%), or both; sometimes neither are present [14,15,19].

GISTs are relatively rare tumors of the GI tract and comprise approximately 5% of all sarcomas [4,14]. These tumors have been reported in dogs [7,11,13], horses [5], rhesus monkeys [2], and a chimpanzee [22] and experimentally in the mouse and rat models [1,8,17]. Earlier findings in *Macaca mulatta* suggest a relationship between simian mesenchymoproliferative disorders (MPD) and GISTs [3]. There are limited data on GISTs in nonhuman primates and we provide first-time reports of GISTs in a baboon and a spider monkey, and a second report of a GIST in a chimpanzee (Table 1).

MATERIALS AND METHODS

Animals

The nonhuman primates were housed in indoor-outdoor metal and concrete cages. They were fed a diet of commercial monkey chow (SWF Primate Diet 3715; Harlan-Teklad, Madison, WI) supplemented with grains, fruits, and vegetables; water was supplied *ad libitum*. All animals at Southwest National Primate Research Center (SNPRC) are cared for in strict compliance with the *Guide for the Care and Use of Laboratory Animals* [18], the Animal Welfare Act, and the Institutional Animal Care and Use Committee of the SNPRC.

Necropsy and Histopathology Evaluation

All three nonhuman primates were necropsied and appropriate tissue samples taken for histologic evaluation. All tissues were fixed in 10% neutral buffered formalin, processed conventionally, embedded in paraffin, cut at 5 microns, stained with hematoxylin and eosin, and evaluated by light microscopy by at least one board-certified veterinary pathologist.

Immunohistochemistry

Immunohistochemistry was performed by using human c-kit (CD117) antibody with appropriate positive and negative controls in all three cases. Formalin-fixed and paraffin-embedded tissue samples from the baboon case were evaluated immunohistochemically. Five-micron representative sections were deparaffinized with xylene and rehydrated in graded alcohols reacted with a commercially available primary antibody for CD117 (1:50 dilution; Dako, Carpinteria, CA) using an automated immunostainer. Immunoreaction was detected according to the manufacturer's instructions (Ventana Medical Systems, Tucson, AZ). Other standard laboratory immunohistochemical methods were performed at the Armed Forces Institute of Pathology (AFIP, Washington D.C.) as needed for each case and may have included c-kit (DAKO Polyclonal Rabbit Anti-Human c-kit, CD117, Code No. A4502, Dako North America, Inc. Carpinteria, CA), desmin (Anti-Desmin (DE-R-11) Primary Antibody, Cat No. 760-2513, Ventana Medical Systems, Tucson, AZ), S-100 (DAKO Rabbit Anti-Cow S100, Code No. Z0311, Dako North America, Inc. Carpinteria, CA), smooth muscle actin (SIGMA Monoclonal Anti-alpha Smooth Muscle Actin, Product No. A 2547, SIGMA-ALDRICH, St Louis, MO), and melan A (MART-1/melan A (A103) prediluted antibody, Ventana Medical Systems, Tucson, AZ). All immunohistochemical tests performed are included in the results section and in Table 1.

RESULTS

Baboon Case Report

A 24-year-old female baboon (*Papio anubis*) was euthanized for degenerative changes and failure to reproduce. Grossly a round, firm mass 2 cm in diameter elevated the mucosa at the cardia of the stomach (Figure 1A). The mass was the same color and consistency as the

stomach mucosa and difficult to visualize. Microscopic evaluation revealed that the mass was composed of loosely arranged spindle cells with prominently vacuolated cytoplasm that formed irregular flowing patterns and tracts (Figure 1C). The neoplastic cells were diffusely positive for c-kit and smooth muscle actin and negative for S-100 upon immunohistochemical staining (Figure 1D). Other incidental lesions were multifocal herniations in the colon and adenomyosis of the uterine wall.

Spider Monkey Case Report

A 25-year-old black male spider monkey (*Ateles paniscus*) was euthanized after a viral hepatitis study. Grossly, a nodule approximately 3 cm in diameter projected from the mid-gastric mucosa. The nodule was firm and white on cut surface (Figure 1B). Microscopic evaluation revealed that the muscular layers of the stomach were expanded by moderately well demarcated, poorly encapsulated infiltrative neoplastic cells forming nests, packets, streams, and bundles. The cells were round to oval, occasionally elongate, and typically had prominent vacuoles within fibrillar amphophilic cytoplasm. The nuclei were round with stippled chromatin. Neoplastic cells were positive for CD117 (c-kit) and negative for S-100 protein, smooth muscle actin, desmin and melan A. No other lesions were found in this nonhuman primate.

Chimpanzee Case Report

A 42-year-old female chimpanzee with a clinical history of ascites, icterus, and previous exposure to hepatitis C virus died. An irregular mass was observed to extend from the rectal mucosa. Microscopic evaluation revealed that the neoplasm in the rectum was composed of densely cellular spindle cells arranged in streams and short interlacing bundles that infiltrated and effaced the submucosa and tunica muscularis. The nuclei were fusiform with finely stippled chromatin and variably sized distinct nucleoli. The neoplastic cells were diffusely positive for c-kit and negative for desmin upon immunohistochemical staining. Concurrently, hepatocellular carcinoma was diagnosed in the liver and gallbladder with metastasis to the kidney, lung, and regional lymph nodes.

DISCUSSION

Historically many GISTs were classified as leiomyomas, leiomyosarcomas, leiomyoblastomas, and gastrointestinal autonomic nerve tumors. A retrospective study of canine leiomyosarcomas using immunohistochemistry revealed that more than 50% were GISTs [21]. GISTs show different morphologies histologically: nearly 70% are composed of spindle cells, 20% epithelioid cells, and 10% of mixed populations of spindle and epithelioid cells.

Since nearly all GISTs express c-kit and many GISTs show mutations in the *c-kit* gene, GIST is now a clear diagnostic entity in human medicine [10]. Diffuse, strong c-kit expression is considered an important factor in diagnosing human GISTs. Some tumors with PDGFRA mutations may show weak CD117 expression [12]. Even though these tumors are positive for c-kit, they have varied responses to other cell markers such as desmin, S-100 protein, and smooth muscle actin [16]. This is consistent with the results in these cases with the baboon demonstrating positive, and the spider monkey negative, results for smooth muscle actin.

In this report the baboon GIST was positive for smooth muscle actin, which is consistent with earlier findings in humans [16]. It is interesting to note that five of the seven GISTs in nonhuman primates have been found in the stomach. When evaluating mesenchymal tumors

of the GI tract in nonhuman primates, GISTs should be considered in the differential diagnosis.

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Figure 1.

Gross appearance of GISTs in the stomach of a baboon (A) and a spider monkey (B). C, Microscopic appearance of a GIST composed of flowing spindle cells with vacuolated cytoplasm in a baboon (H&E, Bar = 200 µm). D, Immunohistochemistry of CD117 reaction in a baboon (Bar = 100 µm) that is characteristic of GIST; note the cells stained brown, which indicates an immunopositive reaction to CD117 (c-kit).

Table 1

GISTs reported in nonhuman primates

Species	Sex	Age (yr)	Clinical history	Location	Immunopositivity	Immunonegativity	Reference
<i>Macaca mulatta</i>	F	10	Microcytic anemia, terminally ill	Stomach	S-100, vimentin ¹	Actin, desmin	[2]
<i>Macaca mulatta</i>	F	24	Microcytic anemia, terminally ill	Stomach	S-100, vimentin ¹	Actin, desmin	[2]
<i>Macaca mulatta</i>	?	5.5	CD4 ⁺ depletion, SIV infection	Colon and rectum	CD117, vimentin	CD31, CD68, desmin and smooth muscle actin	[3]
<i>Pan troglodytes</i>	M	22	Hepatitis C virus infection	Stomach	Diffusely CD117 and CD34 Focally α -smooth muscle actin	Muscle specific actin, desmin, S-100 protein, synaptophysin, and glial fibrillary acidic protein	[22]
<i>Papio anubis</i>	F	24	Weight loss	Stomach	CD117, smooth muscle actin	S-100 protein	
<i>Ateles paniscus</i>	M	25	Woolly monkey hepatitis B virus infection	Stomach	CD117	S-100 protein, smooth muscle actin, desmin, melan A	
<i>Pan troglodytes</i>	F	42	Hepatitis C virus infection	Rectum	CD117	desmin	

¹ c-kit was not identified at the time of publication