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Endocrine neoplasia in New World primates

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Abstract: Of 1,106 New World primates necropsied from the National Zoological Park (Washington, D.C.) and the Department of Comparative Pathology, Johns Hopkins University School of Medicine (Baltimore, Maryland) 22 (1.9%) animals were identified with 27 neoplasms. Of this group, nine animals (two females, seven males) had a total of 13 endocrine neoplasms. All animals were adults, with an age range of 2.7–25 years (average, 12.1 years). Seven were Callitrichidae and two were Cebidae. The adrenal gland was the most affected organ, with seven (53.8%) neoplasms, followed by the pituitary and thyroid gland with two (15.4%) cases each, and the pancreas and parathyroid gland with one tumor (7.7%) each. All neoplastic disorders were benign. Immunocytochemistry assays for growth hormone, adrenocorticotropic hormone, prolactin, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, and chromogranin A were performed on two pituitary neoplasms. Pheochromocytoma was the most frequent neoplasm, representing 5 (38.4%) of the 13 neoplasms. The remaining were thyroid cystadenoma (two, 15.4%), corticotrophic cell pituitary adenoma (two, 15.4%), adrenal ganglioneuroma (one, 7.7%), adrenal cortical adenoma (one, 7.7%), parathyroid chief-cell adenoma (one, 7.7%), and pancreatic islet-cell adenoma (one, 7.7%).

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Introduction

Early reports suggest that neoplastic processes have been infrequent in nonhuman primates [11, 12]. It has been noted that, as of 1968, there were only 122 reported cases of spontaneous neoplasms in monkeys [1]. During the past two decades, the overall number of reported tumors among nonhuman primates has increased remarkably [1, 12]. In part this situation can be explained by the improvement of animal living conditions at zoos and in primate research centers, which accounts for longer life spans in many of the species. Also, pathologic studies in most institutions have improved with complete gross and histopathological evaluation of all deceased animals [15, 24]. Because of their close phylogenetic relationship, the study of neoplasms in nonhuman primates can provide important comparative information for the human counterpart.

The information available on neoplasms arising from the endocrine system in New World nonhuman primates is remarkably scant. Spontaneous adrenal adenomas have been described in mantled howler monkeys (*Alouatta villosa*) and black howler monkeys (*Alouatta caraya*) [8, 13]. One review on neoplasia of nonhuman primates reported a thyroid adenoma in a squirrel monkey (*Saimiri sciureus*), a benign "adrenal tumor" in an owl monkey (*Aotus trivirgatus*), and multiple endocrine neoplasms, composed of a thyroid chief cell adenoma, a pheochromocytoma, and an islet cell adenoma, in a mantled howler monkey [12]. Additional endocrine tumors reported included a pituitary adenoma in a golden lion tamarin [8], adrenal myelolipoma in cottontop tamarins [17, 21, 23], and islet cell adenomas in saddle-backed tamarins (*Saguinus fuscicollis*) [2, 9, 12] and spider monkey (*Ateles geoffroyi*) [6]. A thyroid adenocarcinoma also occurred in a white-lipped marmoset (*Saguinus nigricollis*) [26].

The purpose of this study is to describe 13 endocrine neoplasms in nine animals from two fami-

lies of New World primates. This will include clinical manifestation and immunohistochemistry of two pituitary tumors.

Materials and methods

A total of 1,106 necropsies of New World primates were evaluated, with 871 from the primate colonies of the National Zoological Park (NZP) (Washington, D.C.) and 235 from the research colonies of the Johns Hopkins University School of Medicine (JHU) (Baltimore, MD). Six species of Cebidae and 12 species of Callitrichidae were represented. Animals died naturally or were euthanized, and underwent complete postmortem examinations. Specimens from all organs were fixed in 10% buffered formalin, embedded in paraffin, sectioned at 4–6 μm, and stained with hematoxylin and eosin (HE). Special stains were performed selectively in some cases, including periodic acid Schiff (PAS), PAS-orange G, and Gomori's chrome alum-hematoxylin-phloxine.

Immunocytochemistry was performed on two pituitary adenomas using a method previously described [25]. Briefly, the antigens investigated were growth hormone (GH), adrenocorticotrophic hormone (ACTH), prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), and chromogranin A (CRG). Polyclonal antibodies to GH, ACTH, PRL, FSH, LH, and TSH were obtained from Dako (Carpenteria, CA). The monoclonal antibody to CRG was acquired from Boehringer-Mannheim Biochemicals (Indianapolis, IN). Immunocytochemistry assays were achieved by the avidin-biotin complex (ABC) method [10]. Sections were deparaffinized and rehydrated. The endogenous peroxidase activity was blocked by incubating the tissues in a solution of 3% hydrogen peroxide in methanol for 30 minutes. The sections were left overnight at 4°C in a solution of 10% normal horse serum in 0.01 M phosphate-buffered saline, pH 7.4 (PBS) for the CRG assay, and in 10% normal goat serum in PBS for all others. Sections were incubated with primary antibody for 30 minutes, and subsequently by biotinylated horse–anti-mouse immunoglobulin and ABC (Vector Laboratories, Burlingame, CA) for the CRG monoclonal assay, and biotinylated goat–anti-rabbit immunoglobulin and ABC for all of the polyclonal antibody assays. The chromagen utilized was a solution of 0.024% hydrogen peroxide and 0.016% diaminobenzidine tetrahydrochloride (Sigma Chemical, St. Louis, MO). Slides were counterstained with hematoxylin. Positive and negative control tissues were stained with each batch. The neoplasms were classified according to their gross and microscopic characteristics, primary sites, presence of metastasis, and/or invasive ability [3].

Results

Epidemiology

Of 1,106 New World primates examined, 22 individuals had 27 neoplasms affecting most organ systems. Of this group, 9 were identified with 13 endocrine neoplasm. Eight animals had one primary endocrine neoplasm, two had two, and one had three different types of primary endocrine tumors (Table 1). of the nine affected nonhuman primates, seven (77.7%) were male and two (22.3%) were female. All animals were adults, ranging from 2.7 to 25 years, and the average age was 12.1 years. Seven Callitrichidae had eight (61.5%) neoplasms, and two Cebidae had five (38.5%). Table 1 shows the species, numbers, and gender of platyrrhines affected and corresponding neoplasms.

Endocrine tumors were responsible for 48.1% (13/27) of all neoplasms in platyrrhines. The adrenal was the most affected gland with seven (53.8%) neoplasms, followed by the hypophysis and thyroid gland with two (15.4%) each. The pancreas and parathyroid gland each had one tumor (7.7%). All tumors were classified as benign.

Case reports

Case 1. This was a case of thyroid cystadenoma in a female, 4 year and 11 month old black-tailed marmoset. This marmoset was noted to have abnormal behavior and a protruding upper left canine tooth. It died due to *Pasteurella multocida* septicemia arising from a tooth abscess. Grossly, the endocrine glands were unremarkable. On microscopic examination, the thyroid gland had a sharply demarcated and encapsulated papillary proliferation lined by well-differentiated cuboidal cells within a cystic formation filled with proteinaceous fluid. The neoplasm was diagnosed as a thyroid papillary cystadenoma.

Case 2. This was a case of adrenal cortical adenoma in a female, 8 year and 3 month old black-tailed marmoset. This marmoset presented with weakness, polyphagia, weight loss, and muscle atrophy. Osteoporosis was diagnosed on radiographic examination, and clinical pathological studies revealed hypocalcemia (5.8 mg/dl; normal range, 9.0–10.5 mg/dl) elevated alkaline phosphatase (1,675 IU; normal range, 3.6–39.9 IU) and cortisol (841 IU; value obtained in a clinically normal adult female sibling, 91 IU) levels. Due to the poor prognosis, euthanasia was performed. Gross necropsy revealed marked

Table 1. Endocrine neoplasia in New World primates: Distribution by family, species, sex, and type of neoplasm

Case no.	Species	Sex	Neoplasm
Callitrichidae			
1	Black-tailed marmoset	f	Thyroid, cystadenoma
2	Black-tailed marmoset	f	Adrenal, cortical adenoma
3	Black-tailed marmoset	m	Thyroid, cystadenoma
4	Golden lion tamarin	m	Adrenal, pheochromocytoma
5	Golden lion tamarin	m	Adrenal, pheochromocytoma
6	Golden lion tamarin	m	Pituitary, adenoma
7	Golden lion tamarin	m	Adrenal, pheochromocytoma, adrenal, ganglioneuroma
Cebidae			
8	Mantled howler monkey	m	Pancreas, adenoma, adrenal, pheochromocytoma, parathyroid, adenoma
9	Brown spider monkey	m	Adrenal, pheochromocytoma, pituitiary, adenoma

Black-tailed marmoset, *Callithrix argentata melanura*; Golden lion tamarin, *Leontopithecus rosalia rosalia*; Mantled howler monkey, *Aloutta villosa*; Brown spider monkey, *Ateles fusciceps*.

emaciation, diffuse muscle wasting, and alopecia. The long bones were thinned, and the maxilla and mandible were soft and easily sectioned. There were multiple fractures of the forelimb and hindlimb. The thoracic vertebral column showed marked kyphoses, and the sternal and caudal rib cages were deformed. The left adrenal gland was enlarged and upon section showed at 3 mm, round pale mass within the cortex. Histologically, the adrenal mass was composed of a well-demarcated focus of highly vacuolated, cortical cells diagnosed as an actively secreting cortical adrenal adenoma. The parathyroid glands were unremarkable.

Case 3. This was a case of thyroid cystadenoma in a male, 11 year and 6 month old black-tailed marmoset. This animal had an acute onset of diarrhea and died 36 hours later due to a diffuse, severe lymphoplasmocytic gastroenteritis. At necropsy, the endocrine glands were grossly unremarkable; however, the thyroid gland showed multiple cystic formations surrounding papillary proliferations lined by well-differentiated cuboidal to cylindrical epithelial cells (Fig. 1), compatible with thyroid papillary cystadenoma.

Case 4. This was a case of pheochromocytoma in a male, 12 year and 3 month old golden lion tamarin. This tamarin was submitted for euthanasia due to chronic renal failure, which progressed to neurological signs. Grossly, the left adrenal was enlarged and, on section, showed disruption of the normal structure and replacement by a round 0.5 mm hemorrhagic friable mass, extending focally through the capsule. The right adrenal and other endocrine glands were unremarkable. The histological examination of the affected adrenal revealed a fairly delimited tissue composed of polyhedral to cylindrical cells arranged in nests, cords, or solid alveoli and surrounded by a delicate connective fibrovascular tissue.

Multifocally, clusters of neoplastic cells compressed the adjacent cortex and perforated the capsule; however, no evidence of extra-adrenal involvement was noted. The finely granular cytoplasm of the neoplastic cells had a variable tinctorial affinity, ranging from pale to bright eosinophilic patterns. Some tumor cell clusters had extensively vacuolated cytoplasm. The nuclei ranged in size from large, round, and centrally placed to variably sized, indented eccentric forms. Mitotic figures were uncom-

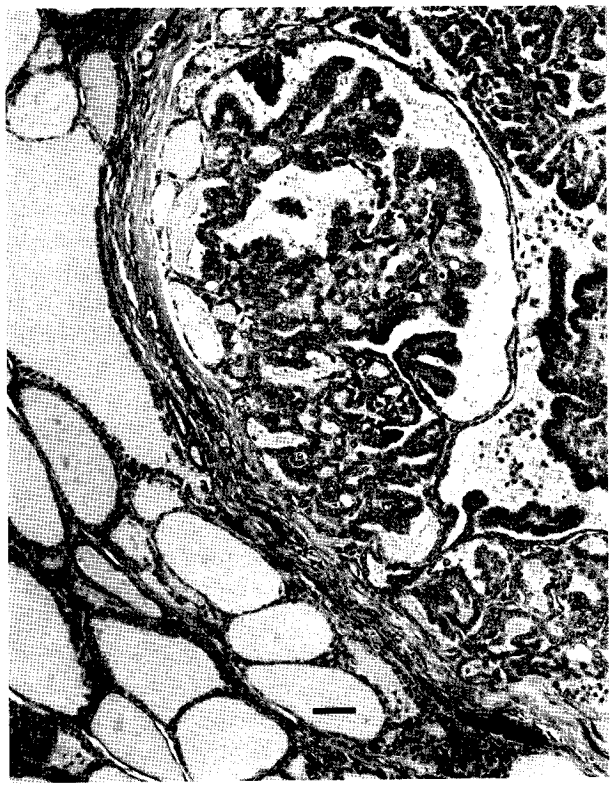

Fig. 1. Thyroid cystadenoma in a black-tailed marmoset, case 3. Cystic formation is surrounding papillary proliferation lined by cuboidal to cylindrical epithelial cells, (HE) Bar = 60 μm.

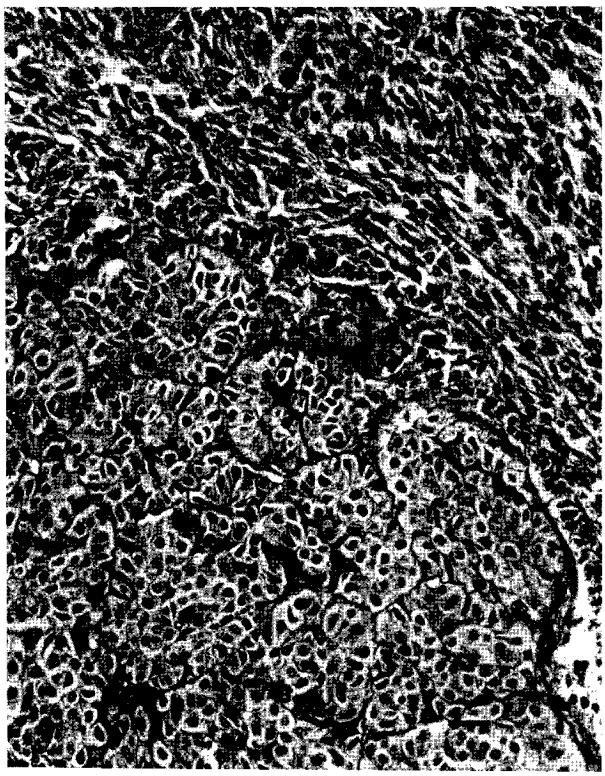

Fig. 2. Corticotrophic cell pituitary adenoma in a golden lion tamarin, case 6. Well-circumscribed mass consisting of follicular structures composed of polyhedral to cuboidal cells. Bar = 40 μm.

mon, at a rate of 0–1/high power field. No evidence of hypertensive changes were noted in the large vessels or the heart.

Case 5. This was a case of pheochromocytoma in a male, 25-year-old golden lion tamarin. Following an acute onset of lethargy and prostration, this tamarin died within four hours of presentation. Pathological findings included acute cholecystitis due to cholelithiasis, which was determined to be the cause of death. Chronic nephropathy and cardiomyopathy associated with aortic atherosclerosis and mural thromboendocarditis were also noted. Grossly, the endocrine glands were unremarkable, but on microscopic examination, the adrenal gland revealed a small pheochromocytoma histologically similar to the one described in case 4.

Case 6. This was a case of corticotrophic cell pituitary adenoma in a male, 2 year and 6 month old golden lion tamarin. The animal was found on the floor, weak and in shock, with no prior signs. Necropsy revealed an extensive traumatic subcutaneous edema and hemorrhages associated with multiple gastric ulcers. Stress combined with hypovolemic cardiac failure were determined as the causes of death. Grossly, the endocrine organs were unremarkable. Histologically, a small, 1 mm in diameter, circumscribed pituitary mass was observed. Histologically, the tumor was composed of uniform-sized follicular structures separated by delicate fibrovascular connective tissue (Fig. 2). The neoplastic cells were medium-sized, polyhedral to cuboidal, and contained variable amounts of small, round eosinophilic granules. The nuclei were small, round- to oval-shaped and centrally located. The mitotic rate was very low, ranging from 0 to 1 mitosis/high power field. Immunocytochemistry assays were strongly positive for ACTH (Fig. 3) and negative for GH, PRL, FSH, LH, TSH, and CRG.

Case 7. This was a case of pheochromocytoma and ganglioneuroma in a male, 18 year and 3 month old, golden lion tamarin. This tamarin was noted to be thin and depressed during a routine physical exam. A mass, located at the cranial ventral abdomen, was palpated but radiographic studies were noncontributory. The animal died during attempts to stabilize its condition. Chronic cholelithiasis leading to cholangitis and atrophic pancreatitis was considered the causes of death. Grossly, the left adrenal gland was replaced by a multilobulated, firm mass, measuring

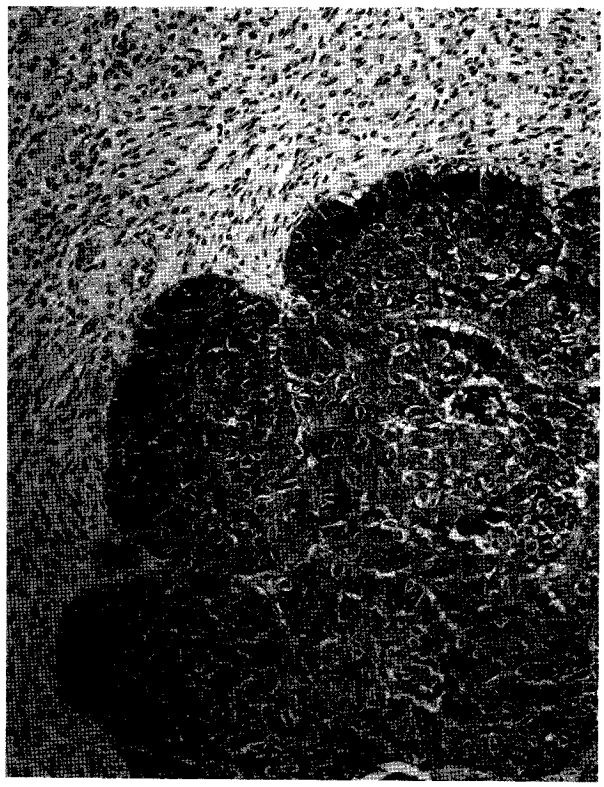

Fig. 3. Corticotrophic cell pituitary adenoma in a golden lion tamarin, case 6. Neoplastic cells are strongly stained for ACTH (avidin biotin peroxidase complex method; hematoxylin counterstain). Bar = 40 μm.

9 mm in diameter. The cut surface of the tumor was pale greyish with a dark red central focus. Histologically, the mass was composed of two distinctive neoplastic cell populations, indicative of pheochromocytoma and ganglioneuroma. The cells were pleomorphic, ranged from spindle to polyhedral in shape, and formed variably sized solid clusters in some areas. These were surrounded by plump, spindle-shaped cells and a large amount of collagen accompanied by clusters of basophilic ganglionic neuronal-like cells (Fig. 4). The mitotic rate was very low, ranging from 0 to 1 mitosis/high power field.

Case 8. This was a case of pheochromocytoma, islet cell adenoma and chief cell adenoma in a male, 14-year-old, mantled howler monkey. This monkey was reported to be thin with depression and anorexia, which progressed to severe liquid diarrhea, vomiting, and severe dehydration. One day prior to death, the animal had a markedly increased coagulation time of several hours. On postmortem examination, ulcerative gastroenterocolitis concomitant with severe interstitial nephritis and glomerulonephritis were considered as the major pathological findings.

The adrenal glands appeared thin and small, with indistinct corticomedullary areas. The remaining endocrine glands were unremarkable. Upon microscopic examination, three benign neoplasms were noted. The parathyroid gland showed several foci of chief cell proliferation, which compressed the adjacent parenchyma and were partially circumscribed by a delicate fibrous capsule. The pancreas showed multiple formations consisting of anastamosing cords of columnar type cells, compatible with islet cell adenoma. The pancreatic exocrine parenchyma was atrophic and showed zymogen granular depletion. The adrenal gland had multiple foci of well-differentiated pheochromocyte proliferation, with extention to the adrenal capsule and compressing the cortex.

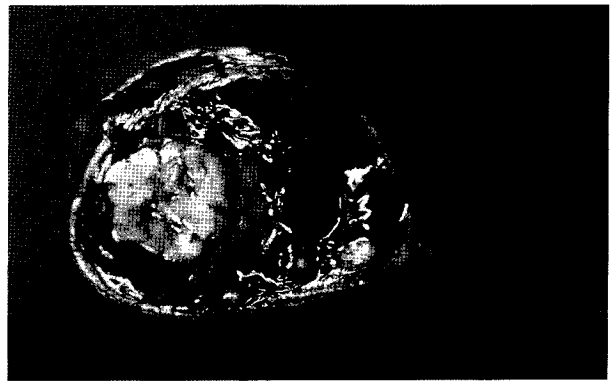

Fig. 5. Adrenal, pheochromocytoma in a brown spider monkey, case 9. The medulla is expanded, containing multiple, variably sized whitish nodules. Areas of hemorrhages are present, and the cortex is atrophied.

Case 9. This was a case of corticotrophic cell pituitary adenoma and adrenal pheochromocytoma in a male, 12 year and 5 month old brown spider monkey. This monkey was reported to have long-term cardiomyopathy, characterized by holosystolic murmurs, cardiomegaly, and extensive pulmonary edema. Despite digitoxin and diuretic therapy, the animal died in cardiac failure. At necropsy, classical features of right-side heart failure, including cardiac interstitial fibrosis, coronary arteriosclerosis, and hepatic chronic-passive congestion, were seen. Grossly, the adrenal glands were bilaterally enlarged; the medullae were markedly expanded, with multiple tan-whitish, firm nodules, up to 0.5 cm in diameter, associated with a multifocal areas of hemorrhages (Fig. 5). The cortices were diffusely atrophied. Histologically, the adrenal neoplasm was defined as a multifocal pheochromocytoma, microscopically similar to the one described in case 4 (Fig. 6).

The pituitary was enlarged (Fig. 7), by 1.5 × 1.3 × 1.0 cm; the right posterior aspect had a focal, reddish black, poorly delimited focus, histologically composed of well-differentiated cuboidal to columnar, granular cells, showing variable basophilic af-

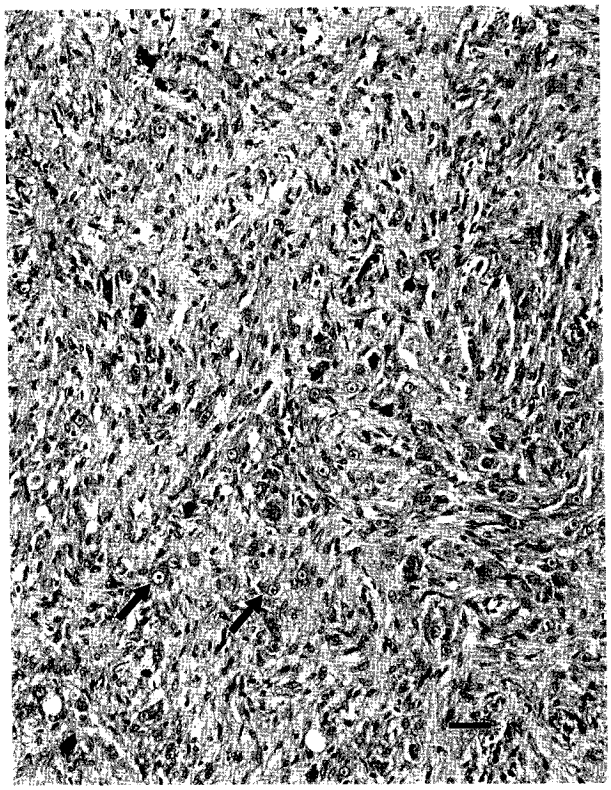

Fig. 4. Adrenal, ganglioneuroma in a golden lion tamarin, case 7. Tumor composed of spindle-shaped cells and collagen associated with clusters of ganglionic neuronal-like cells (arrows) (HE). Bar = 40 μm.

finity. The cells were arranged in a sinusoidal pattern, within a delicate fibrous-vascular framework. Immunocytochemistry assays were diffusely positive for ACTH and negative for GH, PRL, FSH, LH, TSH, and CRG.

Discussion

The documented incidence of endocrine neoplasia in nonhuman primates depends on the species and affected organ. Spontaneous tumors arising in endocrine glands, including pheochromocytoma and pituitary, pancreatic islet cell, adrenal cortex, and thyroid adenomas, were frequently reported in macaques, but uncommon in baboons, guenons, and colobines [12]. Among apes, the same work reported an adrenal cortical adenoma and a thyroid adenoma [12]. The higher occurrence of endocrine neoplasms among macaques was also noted elsewhere [1, 14].

The frequency of occurrence of spontaneous endocrine neoplasia among the New World nonhuman primates is controversial. In a series of 2,176 nonhuman primate necropsies, no endocrine tumors were found among 868 platyrrhines [14]. Similar results were obtained in a series of 288 New World nonhuman primates [22]. In a survey of the major pathological findings among 335 common marmosets, no endocrine tumor was identified [5]. In contrast, endocrine neoplasms were responsible for 11% of all tumors reviewed in New World primates [12].

Fig. 7. Pituitary of a brown spider monkey, case 9, with a corticotrophic cell adenoma. Note the marked enlargement of the gland.

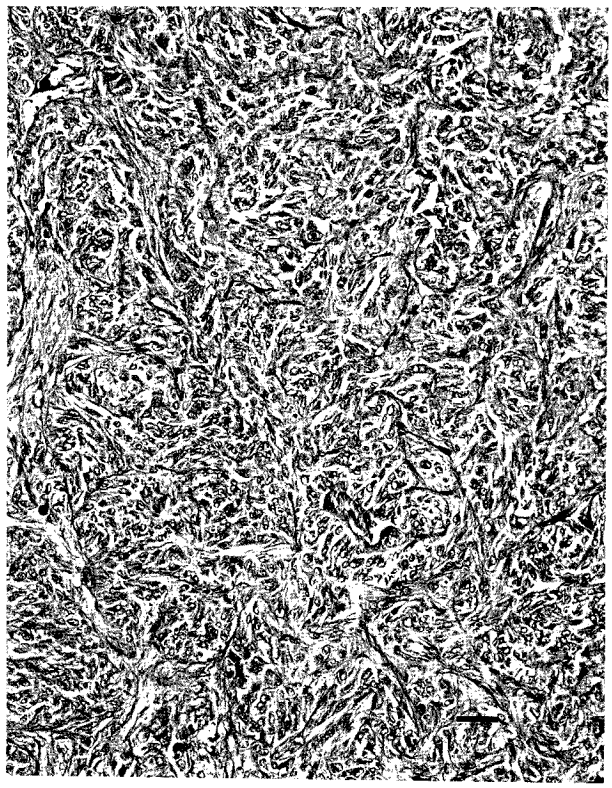

Fig. 6. Adrenal pheochromocytoma in a brown spider monkey, case 9. Nests and cords of neoplastic cells surrounded by a connective fibrovascular tissue (HE). Bar = 40 μm.

In the present study, endocrine neoplasms dominated and accounted for 48.1% of all cases. The reasons for this high incidence is unknown, but two points might be considered. Due to better management conditions, animals were able to have a long life span, with an average age of 12.1 years. It has been proposed that prolonged stimulation of endocrine glands would predispose to a higher incidence of neoplasia [3, 4]. Therefore, it is reasonable to propose that stress that often attends captivity, associated with a longer life span, could have triggered the high endocrine tumor frequency observed. A second aspect is the establishment of complete gross and histopathological procedures, which account for more reliable diagnoses.

Among the endocrine glands, adrenals were the most affected, comprising 53.8% of all tumors. The pheochromocytomas reported in the six cases corresponded to 85.7% of the adrenal neoplasms and