

Case Report

Spontaneous Pituitary Adenomas in Squirrel Monkeys (*Saimiri sciureus*)

Gregory J Daggett Jr,¹ Jennifer S Wood,² Sanjeev Gumber,³ and Christopher J Pinelli,^{3*}

On postmortem examination, 2 geriatric captive male squirrel monkeys (*Saimiri sciureus*) were found to have pituitary masses that were unassociated with previous experimental manipulation. Both animals were euthanized due to apparently unrelated clinical reasons. Histopathology and immunohistochemical staining classified these tumors as thyrotrophic and corticotrophic pituitary adenomas. These cases represent the first reports of this tumor type in squirrel monkeys.

Abbreviation: TSH, thyroid-stimulating hormone

DOI: 10.30802/AALAS-CM-18-000137

Pituitary tumors are a relatively common CNS neoplasm in humans. Antemortem prevalence is difficult to estimate because of the presence of subclinical neoplasms.^{2,11,13,18,19} Pituitary tumors are often classified histologically by the dominant cell type according to immunohistochemical identification of hormonal cell products.²² In NHP, pituitary tumors are reported infrequently in the literature.^{4,5,21,25,28} We here present 2 spontaneous pituitary tumors in squirrel monkeys.

Case History

Both animals were socially housed with conspecifics in an AAALAC-accredited facility (Yerkes National Primate Research Center, Atlanta, Georgia). All aspects of animal care and use noted in this case report were in accordance with the 8th edition of the *Guide for the Care and Use of Laboratory Animals* and the Animal Welfare Act.^{1,10} Both squirrel monkeys were assigned to neuropharmacology protocols, and each had been implanted with a cranial microdialysis chamber and acrylic cap. Neither animal had been on active study for at least 3 y prior to clinical presentation (described later).

Case 1. An 18-y-old male squirrel monkey presented with sudden onset of extreme lethargy and minimal response to stimulation. His previous medical history included 3 skin infections around the acrylic cap between 2002 and 2003; these infections responded to medical management. He had no other recorded medical history. Physical exam at presentation revealed hypothermia, pallor, thin body condition, and severe hypoglycemia. Supportive treatment was initiated, but the animal died shortly after presentation. A definitive cause of death was not evident after postmortem evaluation and histopathologic review, but there was evidence of inanition and metabolic abnormalities (hepatic lipidosis, pancreatic acinar vacuolation, and apoptosis)

which may have contributed to the animal's death. The cause of these changes is unknown.

Case 2. A 19-y-old male squirrel monkey presented for lethargy and dermatitis. He was previously treated for a tooth root abscess, which responded to medical management. He had no other recorded medical history. Physical exam at presentation revealed patchy alopecia along the trunk, arms, and legs; arthritis of the stifles and spine; and considerable urine staining on his hair coat. Diagnostic testing revealed severe hyperglycemia, glucosuria, and mild dehydration. Supportive care was initiated, but the animal was euthanized a few days later due to declining clinical condition. A definitive cause of the clinical signs was not evident prior to euthanasia; the clinical signs may have been a result of the pituitary tumor.

Pathologic findings. In case 1, gross necropsy revealed a mass in the pituitary region; this lesion was approximately 3 to 4 mm in diameter; gray to tan in color; soft; and partially obscuring and replacing the optic chiasm (Figure 1 A). On cut section, the margins were poorly defined and blurred into the normal adjacent cerebral tissue. In case 2, gross necropsy revealed pituitary enlargement within the sella turcica, approximately 0.5 cm in diameter (Figure 1 B). For both cases, tissues were immersion-fixed in neutral-buffered formalin and routinely processed, embedded in paraffin, sectioned at 4 μ m, and stained with hematoxylin and eosin.

Histologic examination of pituitary sections from case 1 revealed a relatively poorly circumscribed mass composed of polygonal cells arranged in sheets and cords and supported by a fine fibrovascular stroma; the lesion was both compressive (Figure 2 A) and locally infiltrative (Figure 2 B). Histologic examination of case no. 2 revealed an expansile, unencapsulated, well-circumscribed, densely cellular neoplasm composed of polygonal cells arranged in nests and packets separated by fine fibrovascular stroma (Figure 2 C). Both tumors had similar morphologic characteristics. Neoplastic cells had well-defined borders with moderate amounts of granular eosinophilic cytoplasm, round to oval nuclei with evenly distributed chromatin, inconspicuous or a single centrally located small magenta nucleolus, and no mitoses detected. Occasionally neoplastic cells

Received: 26 Nov 2018. Revision requested: 26 Jan 2019. Accepted: 22 Apr 2019.

¹Veterinary Services Unit, Wisconsin National Primate Research Center, University of Wisconsin, Madison, Wisconsin; ²Division of Animal Resources, Yerkes National Primate Research Center, Emory University, Atlanta, Georgia; ³Division of Pathology, Yerkes National Primate Research Center, Emory University, Atlanta, Georgia

*Corresponding author. Email: cpinelli@emory.edu



Figure 1. Gross necropsy findings demonstrating spontaneously occurring pituitary adenomas in 2 squirrel monkeys (*Saimiri sciureus*). (A) In case 1, the mass in the pituitary region (hashed circle) is gray to tan, soft, and partially obscures and replaces the optic chiasm. (B) Case 2 demonstrates pituitary enlargement within the sella turcica.

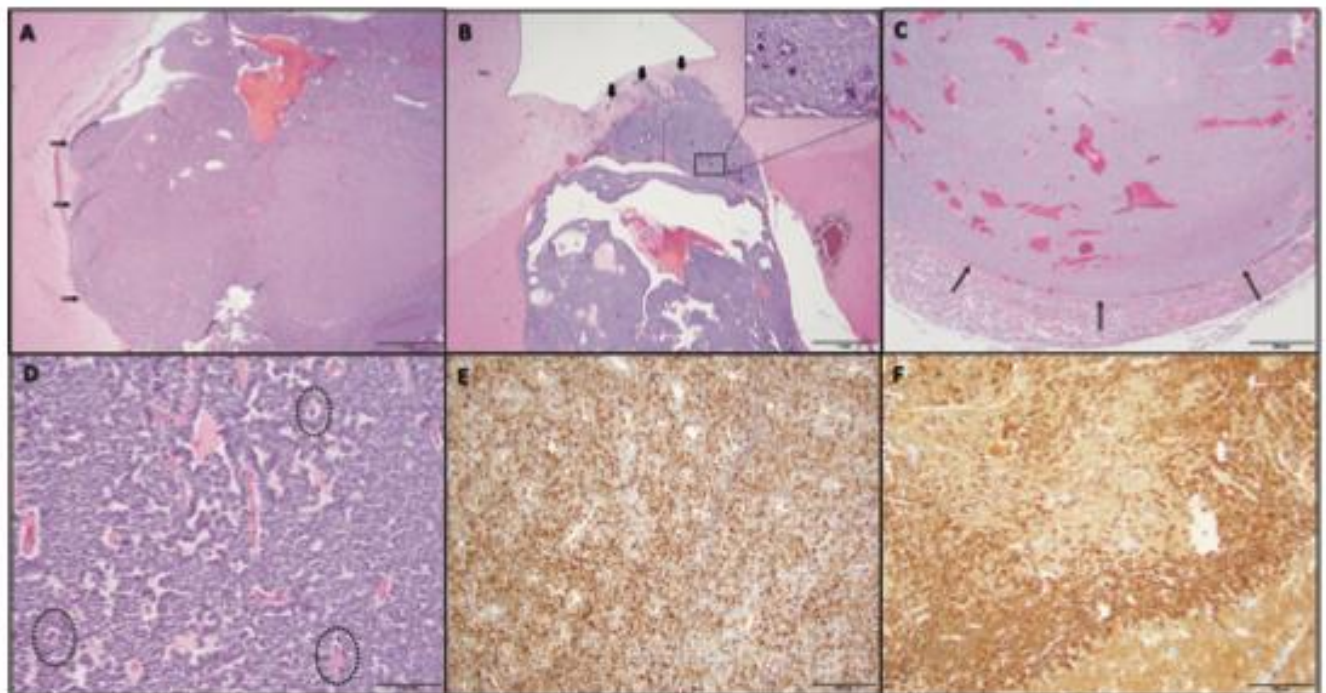


Figure 2. Microscopic findings of spontaneous pituitary adenomas in 2 squirrel monkeys (*Saimiri sciureus*). (A) The tumor in case no. 1 is unencapsulated and compresses the adjacent neuropil; scale, 1 mm. (B) The tumor in case no. 1 is also relatively poorly circumscribed and locally infiltrative, which led to the morphologic diagnosis of invasive pituitary adenoma; scale, 1 mm. (C) The tumor in case 2 is expansile, unencapsulated, and well-circumscribed, leading to the morphologic diagnosis of pituitary adenoma; scale, 50 μ m. Both tumors are densely cellular and composed of polygonal cells arranged in sheets and cords, supported by a fine fibrovascular stroma, and (D) occasionally forming pseudorosettes (hashed lines); scale, 100 μ m. The tumor in case no. 1 also produced psammoma bodies (B, insert). (E) Immunohistochemical staining for thyroid-stimulating hormone in case 1 yielded strong cytoplasmic labeling of more than 90% of neoplastic cells; scale, 200 μ m. (F) In case 2, staining for ACTH yielded diffuse moderate to strong cytoplasmic labeling of neoplastic cells; scale, 200 μ m.

palisaded around blood vessels and formed pseudorosettes (Figure 2 D). In addition, the tumor from case no. 1 contained multiple foci of irregular, deeply basophilic crystalline material (psammoma bodies; Figure 2 B, insert) and occasional regions of necrosis. Local invasion into the adjacent cerebral parenchyma led to the diagnosis of invasive adenoma for case 1, according to the WHO classification of pituitary tumors,^{6,12} whereas case 2 was diagnosed as an adenoma.

To subclassify these tumors, unstained charged slides were submitted to Emory University Hospital to undergo immunohistochemical staining for thyroid-stimulating hormone (TSH), adrenocorticotropic hormone, growth hormone, luteinizing hormone, follicle-stimulating hormone, and prolactin. Neoplastic cells in the tumor from case 1 yielded strong cytoplasmic labeling of more than 90% of neoplastic cells for TSH (Figure 2 E). All other immunostains were negative for this tumor, leading to

the final diagnosis of invasive thyrotrophic pituitary adenoma. Immunostaining of the tumor from case 2 yielded diffuse moderate to strong cytoplasmic labeling of neoplastic cells for ACTH (Figure 2 F). All other immunostains were negative for this tumor, leading to the final diagnosis of corticotrophic pituitary adenoma.

Discussion

To our knowledge, these cases represent the first reports of spontaneous pituitary tumors in squirrel monkeys. Pituitary tumors are uncommon in NHP and, because they are often clinically silent, are primarily diagnosed at necropsy. Historic colony reviews have yielded the most information concerning these neoplasms among laboratory-housed NHP. In a retrospective review of a cynomolgus macaque (*Macaca fascicularis*) colony, pituitary adenomas were identified in 14 of 491 necropsied animals during a 10-y period.²¹ Another medical record review for spontaneous neoplasms in 2 large rhesus macaque (*M. mulatta*) colonies comprising a combined 49 y of records yielded only 6 pituitary tumors.²⁵ Another facility identified 30 pituitary tumors in baboons (*Papio* spp.) over a 15-y period, with an average colony size of 4000 animals.⁵ Of 105 spontaneous neoplasms in chimpanzees reported in the literature, only 4 pituitary adenomas were identified.⁴ Nearly all reported NHP pituitary neoplasms have been histologically classified as adenomas, without distinguishing between invasive and noninvasive subtypes;^{4,5,21,25,28} a lone case report of a pituitary carcinoma was described in an anubis baboon.⁷ Described histologic features of pituitary adenomas were morphologically similar to those in the present cases. In humans, pituitary carcinomas comprise 0.1% to 0.2% of all pituitary tumors and require distant metastasis or entry into the cerebrospinal tract for a diagnosis of carcinoma over invasive adenoma.^{6,9,12,23}

Pituitary tumors are often classified by whether they are functional and by the hormone produced by the neoplastic cell type.^{14,22,27} A previous study characterizing pituitary adenomas in cynomolgus macaques identified lactotrophic, somatotrophic, corticotrophic, and plurihormonal adenomas.²¹ The immunohistochemical profile of the tumor in case 1 identified thyrotrophs as the predominant cell type, with more than 90% of neoplastic cells yielding strong cytoplasmic labeling with TSH immunostaining. The animal showed no clinical signs of central hyperthyroidism, suggesting that this tumor was hormonally nonfunctional. Nonfunctional thyrotrophic tumors with positive TSH immunoreactivity are well documented in humans and are more common than their functional counterparts.^{26,29} In case 2, the immunohistochemical profile revealed predominantly corticotrophs, consistent with the diffuse ACTH immunostaining. We attempted to measure serum cortisol on case 2 by using blood collected prior to euthanasia, however the previously reported values for normal squirrel monkey serum cortisol^{16,24} exceeded the detection limit of the assay used to assess our samples, thus yielding inconclusive results. The immunohistochemical profile for case 2 suggests that the pituitary tumor may have been responsible for the clinical signs, but we were unable to definitively confirm this association. Overall, thyrotrophic adenomas represent only 1% to 2% of reported human pituitary adenomas reported, whereas corticotrophic adenomas have been reported to account for between 5% to 17%.^{3,7,17,20,22} Recent advancements in transcription factor analysis have enhanced classification of nonfunctional adenomas in humans and suggest slightly higher prevalence rates for both tumor types than previously reported.^{25,17} The literature includes 2 case reports of thyrotrophic adenomas and 3 corticotrophic

adenomas occurring in cynomolgus macaques.^{21,28} Galactorrhea was appreciated in one cynomolgus macaque with a corticotrophic adenoma, whereas the remaining 4 animals lacked reported clinical signs.^{21,28} Added to those reports are the current cases of a nonfunctional invasive pituitary thyrotrophic adenoma and a potentially functional corticotrophic adenoma in squirrel monkeys.

Acknowledgments

We thank Fawn Stroud, Elizabeth Strobert, and Joyce Cohen for their expertise and review of the manuscript. The Yerkes National Primate Center is supported by the NIH, Office of Research Infrastructure Programs, Office of the Director (P51OD011132).

References

1. **Animal Welfare Act as Amended.** 2013. 7 USC §2131–2159.
2. **Aron DC, Howlett TA.** 2000. Pituitary incidentalomas. *Endocrinol Metab Clin North Am* 29:205–221. [https://doi.org/10.1016/S0889-8529\(05\)70124-9](https://doi.org/10.1016/S0889-8529(05)70124-9).
3. **Azzalin A, Appin CL, Schniederjan MJ, Constantin T, Ritchie JC, Veledar E, Oyesiku NM, Ioachimescu AG.** 2016. Comprehensive evaluation of thyrotropinomas: single-center 20-year experience. *Pituitary* 19:183–193. <https://doi.org/10.1007/s11102-015-0697-7>.
4. **Brown SL, Anderson DC, Dick EJ Jr, Guardado-Mendoza R, Garcia A, Hubbard GB.** 2009. Neoplasia in the chimpanzee (*Pan spp.*). *J Med Primatol* 38:137–144. <https://doi.org/10.1111/j.1600-0684.2008.00321.x>.
5. **Ciacciolo RE, Butler SD, Eggers JS, Dick EJ, Leland MM, De La Garza M, Brasky KM, Cummins LB, Hubbard GB.** 2007. Spontaneous neoplasia in the baboon (*Papio* spp.). *J Med Primatol* 36:61–79. <https://doi.org/10.1111/j.1600-0684.2006.00202.x>.
6. **DeLellis RA, Lloyd RV, Heitz PU, Eng C, editors.** 2008. Pathology and genetics of tumours of endocrine organs: WHO classification of tumours. Information presented in this book reflects the views of a working group that convened for an editorial and consensus conference presented in Lyon, France, 23–26 April 2003. IARC Press.
7. **Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, McCutcheon IE.** 2004. The prevalence of pituitary adenomas. *Cancer* 101:613–619. <https://doi.org/10.1002/ncr.20412>.
8. **Goodhart JF.** 1885. Cancer of the pituitary body in the anubis baboon. *Transactions of the Pathological Society of London* 36:36.
9. **Heaney AP.** 2011. Pituitary carcinoma: difficult diagnosis and treatment. *J Clin Endocrinol Metab* 96:3649–3660. <https://doi.org/10.1210/jc.2011-2031>.
10. **Institute for Laboratory Animal Research.** 2011. Guide for the care and use of laboratory animals, 8th ed. Washington (DC): National Academies Press.
11. **Jaffe CA.** 2006. Clinically non-functioning pituitary adenoma. *Pituitary* 9:317–321. <https://doi.org/10.1007/s11102-006-0412-9>.
12. **Kiupel M, Capen C, Miller M, Smedley R.** 2008. Histological classification of tumors of the endocrine system of domestic animals. Washington (DC): Armed Forces Institute of Pathology (US).
13. **Klibanski A, Zervas NT.** 1991. Diagnosis and management of hormone-secreting pituitary adenomas. *N Engl J Med* 324:822–831. <https://doi.org/10.1056/NEJM199103213241207>.
14. **Kovacs K, Horvath E, Vidal S.** 2001. Classification of pituitary adenomas. *J Neurooncol* 54:121–127. <https://doi.org/10.1023/A:1012945129981>.
15. **Lopes MBS.** 2017. The 2017 World Health Organization classification of tumors of the pituitary gland: a summary. *Acta Neuropathol* 134:521–535. <https://doi.org/10.1007/s00401-017-1769-8>.
16. **Lyons DM, Ha CM, Levine S.** 1995. Social effects and circadian rhythms in squirrel monkey pituitary–adrenal activity. *Horm Behav* 29:177–190. <https://doi.org/10.1006/hbeh.1995.1013>.
17. **Metz O, Cintosun A, Pressman I, Asa SL.** 2018. Epidemiology and biomarker profile of pituitary adenohypophysial tumors. *Mod Pathol* 31:900–909. <https://doi.org/10.1038/s41379-018-0016-8>.
18. **Molitch ME, Russell EJ.** 1990. The pituitary “incidentaloma”. *Ann Intern Med* 112:925–931. <https://doi.org/10.7326/0003-4819-112-12-925>.

19. Nilsson B, Gustavsson-Kadaka E, Bengtsson BA, Jonsson B. 2000. Pituitary adenomas in Sweden between 1958 and 1991: incidence, survival, and mortality. *J Clin Endocrinol Metab* 85:1420–1425.
20. Raappana A, Koivukangas J, Ebeling T, Pirilä T. 2010. Incidence of pituitary adenomas in Northern Finland in 1992–2007. *J Clin Endocrinol Metab* 95:4268–4275. <https://doi.org/10.1210/jc.2010-0537>.
21. Remick AK, Wood CE, Cann JA, Gee MK, Feiste EA, Kock ND, Cline JM. 2006. Histologic and immunohistochemical characterization of spontaneous pituitary adenomas in fourteen cynomolgus macaques (*Macaca fascicularis*). *Vet Pathol* 43:484–493. <https://doi.org/10.1354/vp.43-4-484>.
22. Saeger W, Lüdecke DK, Buchfelder M, Fahlbusch R, Quabbe HJ, Petersenn S. 2007. Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. *Eur J Endocrinol* 156:203–216. <https://doi.org/10.1530/eje.1.02326>.
23. Sav A, Rotondo F, Syro LV, Di Ieva A, Cusimano MD, Kovacs K. 2015. Invasive, atypical and aggressive pituitary adenomas and carcinomas. *Endocrinol Metab Clin North Am* 44:99–104. <https://doi.org/10.1016/j.ecl.2014.10.008>.
24. Scammell JG, Westberry JM, Sadosky PW, Hubler TR, Williams LE, Gibson SV, Singh RJ, Taylor RL, Shackleton CH. 2006. Cortisol metabolism in the Bolivian squirrel monkey (*Saimiri boliviensis boliviensis*). *Comp Med* 56:128–135.
25. Simmons HA, Mattison JA. 2011. The incidence of spontaneous neoplasia in two populations of captive rhesus macaques (*Macaca mulatta*). *Antioxid Redox Signal* 14:221–227. <https://doi.org/10.1089/ars.2010.3311>.
26. Tritos NA, Eppakayala S, Swearingen B, Hedley-Whyte ET, Miller KK, Nachtigall LB, Grinspoon SK, Biller BM, Klibanski A. 2013. Pathologic and clinical features of pituitary adenomas showing TSH immunoreactivity. *Pituitary* 16:287–293. <https://doi.org/10.1007/s11102-012-0419-3>.
27. Trouillas J, Roy P, Sturm N, Dantony E, Cortet-Rudelli C, Vienne G, Bonneville J-F, Assaker R, Auger C, Brue T, Cornelius A, Dufour H, Jouanneau E, François P, Galland F, Mougel F, Chapuis F, Villeneuve L, Maurage CA, Figarella-Branger D, Raverot G; members of HYPOPRONOS, Barlier A, Bernier M, Bonnet F, Borson-Chazot F, Brassier G, Caulet-Maugendre S, Chabre O, Chanson P, Cottier JF, Delemer B, Delgrange E, Di Tommaso L, Eimer S, Gaillard S, Jan M, Girard JJ, Lapras V, Loiseau H, Passagia JG, Patey M, Penfornis A, Poirier JY, Perrin G, Tabarin A. 2013. A new prognostic clinicopathological classification of pituitary adenomas: a multicentric case-control study of 410 patients with 8 years postoperative follow-up. *Acta Neuropathol* 126:123–135. <https://doi.org/10.1007/s00401-013-1084-y>.
28. Tsuchitani M, Narama I. 1984. Pituitary thyrotroph cell adenoma in a cynomolgus monkey (*Macaca fascicularis*). *Vet Pathol* 21:444–447. <https://doi.org/10.1177/030098588402100412>.
29. Wang EL, Qian ZR, Yamada S, Rahman MM, Inosita N, Kageji T, Endo H, Kudo E, Sano T. 2009. Clinicopathological characterization of TSH-producing adenomas: special reference to TSH-immunoreactive but clinically non-functioning adenomas. *Endocr Pathol* 20:209–220. <https://doi.org/10.1007/s12022-009-9094-y>.