Case #8

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CONTRIBUTOR(S)/INSTITUTION:

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SIGNALMENT:

- 13 year old, Indian-origin, female rhesus macaque (Macaca mulatta)
- Group-housed in an indoor-outdoor AAALAC-accredited facility (Johns Hopkins Primate Breeding Farm)
- Maintained in accordance with the Animal Welfare Act and the *Guide for the Care and Use of Laboratory Animals*
- Colony is SPF for SIV, simian T-lymphotropic virus, simian retrovirus, and *Macacine herpesvirus 1*

HISTORY:

This animal presented with a history of progressive weight loss, vision loss, and circling to the right over the course of one year. She was lactating, despite not having given birth for two years. Test results over the year are listed below.

- Complete blood count (CBC): stress leukogram
- Chemistry panel: mild hypokalemia.
- Thiamine: WNL
- Serum estrogen (E2): WNL (<5 pg/ml)
- Progesterone (P4): WNL (0.10 ng/ml)
- **Prolactin: elevated (147.6 ng/ml - expected value 20-50 ng/ml)**
- Rectal culture: negative for enteric pathogens.
- Orthopedic examination: WNL
- Abdominal radiographs: WNL
- Abdominal ultrasound: WNL
- Gastrointestinal endoscopy and biopsies of the stomach, small intestine, and colon: lymphoplasmacytic gastroenteritis.

Ophthalmologic exam results:

- **Searching behavior, unable to fix and follow an object or finger**
- **PLR: dull response, mild pupil dilation OU**
- **Optokinetic drum: negative nystagmus**
- Intraocular pressures (Tonopen) WNL (od = 15 mmHg and os = 18 mmHg)
- Fundic exam:
    - **Optic nerve pallor OU**
    - Optic nerve cup:disc ratio 0.1 OU (WNL)
    - Normal caliber and tortuosity of the retinal vessels
    - Apparently healthy macula

MRI results (Pre-and post-contrast T1-weighted, T2-weighted, and STIR images of the head):

- Large (3.2 x 2.9 x 2.5cm), lobulated, mildly septated mass protruding from the pituitary fossa
- Mass extends rostrally from the level just rostral to the optic chiasm, caudally along the ventral aspect of the pons, and dorsally to cause dorsal deviation and compression left lateral ventricle
- Moderate asymmetric dilatation of the lateral ventricles is present, and there is compression of the rostral ventral aspect of the cerebellum
- No other significant structural lesions, abnormal signal, or abnormal contrast enhancement are identified within the cerebrum, thalami, hypophyseal structures, brainstem, and cerebellum
- **Large, avidly contrast-enhancing hypophyseal mass with an associated marked mass effect, most consistent with a pituitary macroadenoma.**

After identifying the mass on MRI, the animal was euthanized with IV sodium pentobarbital and phenytoin solution due to poor prognosis.

GROSS FINDINGS:

- Cerebrum, pituitary adenoma
- Skeletal muscle (whole body), atrophy, chronic, diffuse, severe
- Heart, mitral valve, myxomatous valvular degeneration, chronic, multifocal, mild

HISTOPATHOLOGIC/CYTOLOGIC FINDINGS:

Cerebrum: Expanding and compressing surrounding neuropil is a densely cellular, well-demarcated, nodular, unencapsulated neoplasm. Neoplastic cells are closely packed and are arranged in nests/packets and frequently palisading around blood vessels (pseudorossettes) on a fine fibrovascular stroma. Cells are columnar to polygonal with indistinct cell borders and a scant to moderate amount of eosinophilic granular cytoplasm. Nuclei are round and centrally located with coarsely stippled chromatin and occasional 1-2 prominent nucleoli. Anisocytosis and anisokaryosis are mild. Mitoses are rare (<1 per high powered field). Rarely, tubular structures are filled with an eosinophilic proteinaceous material. Vascular invasion is not appreciated in this section.

ANCILLARY TESTING:

Immunohistochemistry:

- Synaptophysin (+)
- ACTH (-)
- Growth Hormone (-)
- Prolactin (-)
- FSH: (-)
- MSH: (-)

Electron Microscopy:

- Pending

MORPHOLOGIC/ETIOLOGIC DIAGNOSIS:

Pituitary, adenoma, null

DISCUSSION:

Clinical signs in this adult, female Rhesus Macaque are due to a large, compressive tumor at the level of the pituitary gland, with histomorphology consistent with a pituitary adenoma. Immunohistochemistry of the tumor is negative for hormonal production, suggesting that this may be an endocrinologically inactive (aka nonfunctional or null) adenoma. Electron microscopy is pending; the presence of secretory granules will confirm whether this is a prolactin-secreting tumor or not. The most common cause of nonfunctional pituitary tumors in aged animals is chromophobe adenomas arising from the pars distalis.

Clinical signs of nonfunctional adenomas are typically due to expansion of the tumor into the unaffected pituitary and adjacent CNS, leading to decreased secretion of pituitary hormones or CNS dysfunction. For instance, progressive weight loss and muscle atrophy occurs due to decreased growth hormone; gonadal atrophy due to decreased gonadotropic hormones; dilute urine with low specific gravity in the face of dehydration due to decreased antidiuretic hormone. As in this case, animals may develop blindness with fixed, dilated pupils due to dorsal extension of the tumor and compression of the optic nerves. Opthalmic exam is typically otherwise unremarkable because dysfunction is originating from the CNS.

Interestingly, this animal demonstrated clinical signs of hyperprolactinemia (galactorrhea and elevated serum prolactin levels) despite tumor cells having negative immunoreactivity for prolactin. We propose that hyperprolactinemia in this case is due to “stalk syndrome” or “pituitary stalk compression syndrome,” a phenomenon in which non-secretory suprasellar tumors induce hyperprolactinemia by inhibiting dopamine delivery to lactotrophs. Since dopamine is a prolactin-inhibiting factor, reduction of dopamine levels leads to increased prolactin output. It is hypothesized that dopamine levels are reduced by one of two mechanisms: 1) physical compression of the dopaminergic neurons of the infundibular stalk or 2) disruption of hypophyseal portal blood flow which is delivers dopamine to lactotrophs.

In humans, the degree of prolactinemia can provide some clues to help differentiate a prolactinoma from a large tumor with “stalk effect”. Prolactinemia over 200 ng/mL in humans is almost always due to a hormone-producing prolactinoma and not stalk effect. Unfortunately, normal ranges are less well known in rhesus macaques.

Typical lesions of null pituitary adenomas are as follows:

- Large tumor (>1cm) with compression or replacement of the remaining adenohypophysis, infundibular stalk, and hypothalamus
- Small thyroid glands
- Small adrenal glands due to *cortical* atrophy
- Small gonads due to atrophic seminiferous tubules with little active spermatogenesis
- Atrophy of skin and muscle

Panhypopituitarism caused by endocrinologically inactive pituitary adenomas should be a differential in older animals with incoordination, depression, polyuria, blindness, and sudden behavioral changes.

Key to Histologic Diagnosis of Pituitary lesions:

Proliferative pituitary lesions must first be differentiated as non-neoplastic or neoplastic (Table 1). If the lesion is neoplastic, the tissue of origin must be determined (Table 2). Keep in mind that neuroendocrine tumors from other regions of the body may metastasize to the pituitary and thus can be positive for both synaptophysin and chromogranin, therefore other markers may be necessary for differentiation.

The pituitary is made up of at least six different cell types that can give rise to tumors that are clinically functioning or silent. Each of these cell types produce one or more specific hormones that can be targeted via immunohistochemistry (Table 3). Additionally, plurihormonal and hormone negative adenomas can also occur.

Histopathologic and electron microscopic features characteristic of null cell adenomas in humans are:

- Elongated small cells forming pseudorosettes around dilated capillaries
- Modest cytoplasm
- Poorly developed rough endoplasmic reticulum and golgi apparatus
- Rare, round secretory granules

Table 1. Differentials for non-neoplastic pituitary lesions

Hyperplasia
Inflammation (infectious vs immune)
Rathke's cleft cyst
Arachnoid cyst
Meningoencephalocele
Hamartoma
Dermoid / epidermoid cyst

Table 2. Differentials for non-pituitary origin neoplasias

Benign	Malignant
Craniopharyngioma	Gliomas
Gangliocytoma / Ganglioglioma	Germ cell tumor
Granular Cell tumor	Lymphoma
Meningioma	Vascular / mesenchymal
Schwannoma	---
Chordoma	---
Vascular / mesenchymal	Misc (salivary gland, melanoma, etc)

Table 3. IHC Markers for Pituitary Adenomas	
Marker	**Tumor Type**
GH	Somatotroph Adenomas Mammosomatotroph Adenomas
PRL	Lactotroph adenomas Lactotroph adenomas with GH reactivity
TSH	Thyrotroph adenomas
ACTH	Corticotroph adenomas
FSH	Gonadotrophin adenomas

** GH: Growth Hormone, PRL: Prolactin, TSH: Thyroid Stimulating Hormone, ACTH: Adrenocorticotropin Hormone, FSH: Follicle Stimulating Hormone

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