# Excessive production of sex hormones in a cat with an adrenocortical tumor

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**Case Description**—A 13-year-old neutered male domestic shorthair cat was evaluated because it was spraying urine that had a strong odor and had developed aggressive behavior.

**Clinical Findings**—Physical examination did not detect any palpable testes within the scrotum; however, spines were detected on the penis. Abdominal ultrasonography revealed a mass in the region of the right adrenal gland. Results of adrenal hormonal analyses revealed considerable increases in serum concentrations of androstenedione and testosterone.

**Treatment and Outcome**—A mass associated with the right adrenal gland was found during exploratory laparotomy. There was no invasion of the mass into the caudal vena cava. No ectopic gonadal tissue was seen within the abdomen. Adrenalectomy of the right adrenal gland was performed, and histologic evaluation of the mass revealed an adrenocortical adenoma. Two weeks after surgery, serum concentrations of androgens had decreased. Eight weeks after surgery, the cat was no longer spraying urine and was acting affectionate toward the owner.

**Clinical Relevance**—Adrenal gland tumors can produce a variety of hormones other than cortisol. An adrenal gland tumor should be considered in neutered cats with newly developed physical and behavioral changes of a sexual nature. In the absence of debilitating conditions that are often associated with hyperadrenocorticism, cats undergoing adrenalectomy for an adrenal gland tumor that is producing sex hormones may have resolution of clinical signs and a good prognosis. (*J Am Vet Med Assoc* 2009;234:505–508)

A 13-year-old 4.6-kg (10.1-lb) neutered male domestic shorthair cat was evaluated at Dallas Veterinary Surgical Center to determine the cause of urine spraying and aggressive behavior. The cat was acquired by the owner as a kitten from an animal shelter; it was castrated during its stay at the shelter. The owner reported that for approximately 2 years prior to evaluation, the cat had been spraying urine with a strong odor and acting in an aggressive manner. The owner also noticed that the cat's face seemed larger than in previous years and that it had recently lost weight. No changes had been noticed in appetite, water consumption, or volume of urination.

Initial examination revealed that the cat was quiet but alert and responsive. Rectal temperature was 37.4°C (99.4°F). The cat had a pulse rate of 192 beats/min and a respiration rate of 64 breaths/min. The high pulse and respiratory rates were attributed to stress during the hospital visit. No murmur, arrhythmia, or abnormal lung sounds were heard on thoracic auscultation. The cat was thin with a body condition score of 2/5. It had a round face with enlarged masseter and caudal mandibular regions and a thin, coarse hair coat. Examination of the genitalia revealed spines on the penis, but there was a lack of palpable testes within the scrotum. No other abnormalities were detected during physical examination. Differential diagnoses included ectopic gonadal tissue, acromegaly, behavioral disorder, adrenal gland tumor, and hyperthyroidism.

Blood and urine were collected, and thoracic radiography was performed. It was difficult to perform venipuncture because of the thickness of the cat's skin. No abnormalities were detected in the results of a CBC and serum biochemical analysis. The total serum thyroxine concentration was within reference limits (1.56 µg/dL; reference limits, 0.8 to 4.0 µg/dL). Results of urinalysis revealed mild proteinuria and a urine specific gravity of 1.045. Thoracic radiography (left lateral, right lateral, and ventrodorsal radiographic views) revealed no abnormalities.

Abdominal ultrasonography was performed, which revealed a 1.4 × 1.1-cm mixed-echogenic cystic mass in the liver and a 1.8 × 1.2-cm oval soft tissue mass in the region of the right adrenal gland (**Figure 1**). The adrenal mass was immediately adjacent to the caudal vena cava, but invasion of the mass into the caudal vena cava was not detected. The left adrenal gland was of typical size (1.0 × 0.4 cm) and had a normal appearance. No other abnormalities were observed.

An ACTH stimulation test was performed by administering synthetic ACTH[a] (25 µg/kg [11.4 µg/lb], IM).[1] Serum samples were obtained before (baseline) and 30 and 60 minutes after ACTH administration. The serum samples were submitted to the University of Tennessee Clinical Endocrinology Service for measurement of adrenal gland hormone concentrations. Results revealed a baseline serum concentration of cortisol (42.6 ng/mL; reference limits, 9.8 to 59.0 ng/mL) within reference limits, but the serum concentrations of cortisol were less than reference limits at 30 and 60

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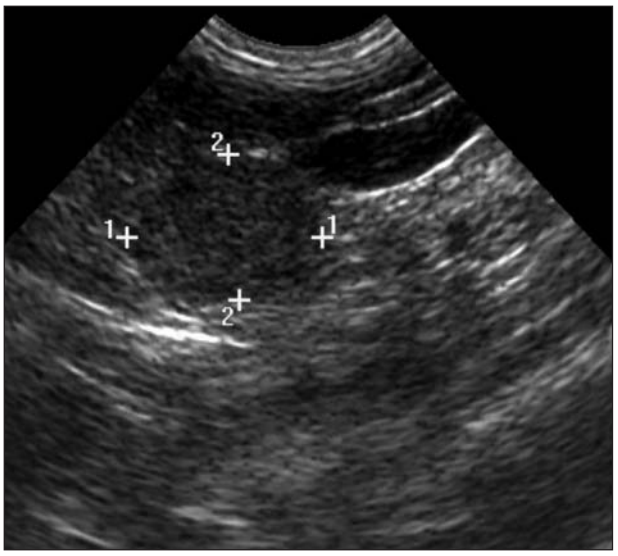


Figure 1—Ultrasonogram of a mass adjacent to the right adrenal gland in a neutered male cat. Margins of the mass are marked by cursors (plus signs). Distance between the cursors was 1.8 cm (pair 1) and 1.2 cm (pair 2).

minutes after ACTH administration (50.0 ng/mL and 38.5 ng/mL, respectively; reference limits, 95.0 to 183.0 ng/mL). Baseline androstenedione concentration was high (> 100 ng/mL; reference limits, 0.7 to 5.5 ng/mL), and concentrations remained high in both samples obtained after ACTH administration (> 100 ng/mL at 30 and 60 minutes; reference limits, 5.2 to 28.0 ng/mL). Similarly, baseline testosterone concentration was high (10.4 ng/mL; reference limits, 0.2 to 0.5 ng/mL) and remained high after ACTH administration (8.6 ng/mL and 8.9 ng/mL at 30 and 60 minutes; reference limits, 0.25 to 0.50 ng/mL). Baseline progesterone concentration was high (1.98 ng/mL; reference limits, 0.06 to 0.70 ng/mL), but concentrations after ACTH administration were within the reference limits (2.77 ng/mL and 2.22 ng/mL at 30 and 60 minutes; reference limits, 0.9 to 4.6 ng/mL). In contrast, baseline 17-hydroxyprogesterone concentration was high (4.24 ng/mL; reference limits, 0.08 to 0.30 ng/mL), and the concentrations remained high after ACTH administration (4.91 ng/mL and 4.57 ng/mL at 30 and 60 minutes; reference limits, 0.2 to 1.6 ng/mL). Baseline concentration of estradiol was within reference limits (70.2 pg/mL; reference limits, 39 to 79 pg/mL), and the estradiol concentration was essentially unchanged after ACTH administration (70.2 pg/mL and 65.7 pg/mL at 30 and 60 minutes; reference limits, 38 to 70 pg/mL). Baseline concentration of aldosterone was within reference limits (37.5 pg/mL; reference limits, 11.3 to 294.3 pg/mL) and increased after ACTH administration (58.9 pg/mL and 69.5 pg/mL at 30 and 60 minutes; reference limits after ACTH administration have not been established).

A diagnosis of a functional adrenal gland tumor was made. Abdominal exploratory surgery was recommended to perform an adrenalectomy and remove the mass in the liver.

The cat was premedicated with hydromorphone (0.08 mg/kg [0.036 mg/lb], IV). Anesthesia was induced with propofol (6.5 mg/kg [2.95 mg/lb], IV) and maintained with inhalation of isoflurane. Midline celiotomy was performed. The right adrenal gland was large (approx 1.5 cm), irregularly shaped, and discolored, and it adhered to the caudal vena cava. The left adrenal gland appeared normal in size and shape. The quadrate lobe of the liver contained a 1.0-cm cystic mass. Exploration of the remainder of the abdomen did not reveal ectopic gonadal tissue or other abnormalities. In the event of a possible cortisol deficiency resulting from suppression of the contralateral adrenal gland, dexamethasone (0.2 mg/kg [0.091 mg/lb], IV) was administered prior to manipulation of the right adrenal gland. The right adrenal gland was gently dissected free from the wall of the vena cava and removed. There was no invasion of the mass into the caudal vena cava. The mass in the liver was also removed, and both tissues were submitted for histologic examination. The abdomen was closed in a routine manner.

The cat recovered in an intensive care unit and was administered a crystalloid solution[b] IV and a continuous rate infusion of fentanyl (2 µg/kg/h [0.91 µg/lb/h]). Administration of dexamethasone (0.2 mg/kg, IV) was repeated the morning after the surgery. The cat was discharged 2 days later with instructions to the owner for administration of tramadol (2.7 mg/kg [1.23 mg/lb], PO, q 12 h for 7 days) and prednisone (0.23 mg/kg [0.104 mg/lb], PO, q 24 h for 5 days, then decreased to q 48 h for 2 weeks).

Histologic examination of the submitted tissues revealed a completely excised, encapsulated adrenocortical adenoma and a completely excised hepatic biliary cystadenoma. The biliary cystadenoma was considered to be benign and to have no relationship to the adrenal gland adenoma.

Two weeks after surgery, the cat was returned to the veterinary surgical center. The owner reported that the cat was doing well at home. The cat was acting less aggressive, and the frequency of urine spraying was greatly decreased. Sutures were removed, and an ACTH stimulation test was repeated by use of the aforementioned protocol. The baseline serum concentrations of androstenedione (1.7 ng/mL) and testosterone (0.05 ng/mL) had decreased to within and less than the respective reference limits. The baseline serum concentration of progesterone (0.55 ng/mL) had also returned to within reference limits, whereas the baseline serum concentration of 17-hydroxyprogesterone (< 0.08 ng/mL) was less than the lower limit of detection of the assay. The baseline serum concentrations of estradiol (69.2 pg/mL) and aldosterone (82 pg/mL) remained within reference limits. The baseline serum concentration of cortisol (51.1 ng/mL) remained within reference limits, but the serum concentrations of cortisol still did not increase at 30 and 60 minutes after ACTH administration (67.9 ng/mL and 53.3 ng/mL, respectively).

Eight weeks after surgery, the cat was no longer spraying urine, and the urine did not have a strong odor. In addition, the cat was acting affectionately toward the owner.

## Discussion

Hyperadrenocorticism is an increased secretion of hormones by the adrenal cortex. This is a rare condi-

tion in cats. Diagnosis is based on the evaluation of patient history and results of physical examination, clinicopathologic analyses, diagnostic imaging, and screening assays for hormone concentrations, such as a urine cortisol-to-creatinine ratio, ACTH stimulation test, and low-dose dexamethasone suppression test. Approximately 80% of affected cats have pituitary-dependent hyperadrenocorticism, and 20% are caused by a functional adrenal gland tumor.[2] Of cats with a functional adrenal gland tumor, 50% have an adrenocortical adenoma, and 50% have a carcinoma.[2]

Hyperadrenocorticism is typically associated with abnormal increases in serum concentrations of glucocorticoids, and the most common clinical signs are polyuria, polydipsia, polyphagia, and alopecia. The skin is also fragile and can be easily bruised or lacerated. Some of these signs may also be attributable to diabetes mellitus; up to 80% of cats with hyperadrenocorticism also have diabetes mellitus.[2] Additional physical examination findings include a pendulous abdomen, muscle wasting, and skin infections. The abnormal hormone concentrations in this cat are somewhat similar to those for hyperadrenocorticism syndrome in ferrets, which primarily involves overproduction of sex hormones.[3]

A reliable medical treatment for hyperadrenocorticism in cats is not currently available. Adrenalectomy (unilateral or bilateral) is an alternative treatment, and it can be successful. However, complications are common and include electrolyte abnormalities, skin lacerations, pancreatitis, hypoglycemia, pneumonia, sepsis, and thromboembolic disease.[4]

The cat reported here did not have clinical signs of typical hyperadrenocorticism, which was supported by the lack of hypercortisolemia. However, there may be clinical signs of hyperadrenocorticism even when there is no increase in the baseline serum concentration of cortisol.[2,5–8] Also, up to 50% of cats with hyperadrenocorticism will not have an increase in serum concentrations of cortisol after ACTH stimulation.[2] Other adrenal gland hormones, such as progestins, have intrinsic glucocorticoid activity with affinity for glucocorticoid receptors and cortisol-binding protein.[5] Increased secretion of these other hormones may explain the typical clinical signs in cats with atypical hyperadrenocorticism that have serum concentrations of cortisol within reference limits.

The physical and behavioral changes in this cat were attributed to increased secretion of androgens originating from an adrenal gland tumor. The lack of typical clinical signs of hyperadrenocorticism in this cat may be explained by the mild increases in serum concentrations of progestins relative to androgens. Neoplastic cells can produce and secrete excessive amounts of various adrenal hormones. Adrenal gland tumors may also have aberrant biosynthetic pathways or enzyme deficiencies. Precursors may accumulate proximal to a blockage in a biosynthetic pathway, with possible redirection of the precursors to other metabolic pathways.[9]

Androstenedione had the greatest relative increase in serum concentrations among all of the adrenal gland hormones evaluated and was considered to be directly produced and secreted by the adrenal gland tumor. However, the exact origin of the increased serum concentration of testosterone was not evaluated. Testosterone may have been produced and secreted directly by the adrenal gland tumor. Another possible origin of the testosterone was conversion of precursors, such as androstenedione, in peripheral tissues.[9,10] Because there was a substantial increase in the serum concentration of androstenedione, it is reasonable to consider peripheral conversion of precursors as the origin of the increased serum concentrations of testosterone.

Cats with increased secretion of progesterone or other sex hormones from an adrenal gland tumor have been reported elsewhere.[6,8,11,12] In 3 of these reports,[6,8,12] cats had increased serum concentrations of progesterone and typical clinical signs of hyperadrenocorticism. In the fourth report,[11] the cat had bilaterally enlarged adrenal glands, increased serum concentrations of testosterone, and similar physical and behavior changes to that of the cat reported here. The cat in the other report[11] had moderate improvements in clinical signs after treatment with trilostane, but later had a recurrence of clinical signs and was subsequently euthanized. Clinical signs resolved following adrenalectomy in a dog with a sex hormone–producing adrenal gland tumor.[7] To our knowledge, the information provided here represents the first report of a cat with an adrenal gland tumor that resulted in substantial increases of only androstenedione and testosterone concentrations. Other animals with increased production and secretion of androgens may have had different outcomes than the cat reported here. It is possible these other animals may have had increased production and secretion of other hormones (such as progesterone and aldosterone), thus causing a state of debilitation. This may have influenced treatment decisions such that medical management was chosen, rather than adrenalectomy. Increased production and secretion of other hormones may have also caused an increase in serious complications following surgical treatment.

The cat reported here had physical and behavioral changes that were attributed to increased production and secretion of androgens induced by an adrenocortical adenoma. Serum samples obtained before and 30 and 60 minutes after ACTH administration were analyzed as a screening test for a functional adrenal gland tumor. In retrospect, an accurate diagnosis may have been possible by evaluating baseline serum concentrations of sex hormones to detect increases above reference limits and not performing an ACTH stimulation test. The cat in this report had considerable improvement in clinical signs, which correlated with a decrease in serum concentrations of androgens following adrenalectomy. The potential for future undesirable behaviors may still exist because they may have become learned behaviors. Cats that undergo gonadectomy as adults are more likely to display behavior problems, such as urine spraying.[13] The cat described in this report was not available for further follow-up physical examination, but the owner reported that the cat's face was not as round and that the size of the masseter and caudal mandibular regions seemed to have diminished, compared with the preoperative appearance. Postoperative physical changes, including regression of penile spines, in this cat would be expected after removal of androgen influences.[14]

An adrenal gland tumor should be considered in any previously neutered cat with newly developed physical changes and signs of sexual behavior. Adrenocortical tumors have the potential to secrete a variety of hormones other than cortisol, including sex hormones and their precursors. In the absence of other debilitating conditions often associated with hyperadrenocorticism, cats undergoing adrenalectomy for an adrenal gland tumor that is primarily producing sex hormones may have resolution of clinical signs and an overall good prognosis.

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b. Normosol-R, Abbott Laboratories, Chicago, IL.

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