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Case Report Rapport de cas

Sex-hormone producing adrenal tumors causing behavioral changes as the sole clinical sign in 3 cats

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Abstract — Three neutered cats with adrenocortical tumors that were presented with behavioral changes but no evidence of hyperaldosteronism or hypercortisolism are described. All 3 cats had resolution of their clinical signs following adrenalectomy. For neutered cats presenting with behavior changes, a sex-hormone secreting adrenal tumor should be considered as a differential diagnosis.

Résumé — Tumeurs surrénaliennes produisant des hormones sexuelles causant des changements de comportement comme seul signe clinique chez 3 chats. Les cas de trois chats stérilisés ayant des tumeurs surrénaliennes qui ont été présentés avec des changements comportementaux mais aucun signe d'hyperaldostéronisme ou hypercortisolisme sont décrits. Les trois chats ont eu une résorption de leurs signes cliniques après une surrénalectomie. Pour les chats stérilisés présentant des changements comportementaux, une tumeur surrénalienne sécrétant des hormones sexuelles devrait être considérée comme un diagnostic différentiel.

(Traduit par Isabelle Vallières)

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Adrenal tumors are rarely reported in cats, with the most common presenting complaints being due to hyperaldosteronism or hypercortisolism (1,2). Common clinical signs in cats with adrenal tumors include hypokalemic polymyopathy and hypertension-induced blindness associated with hyperaldosteronism and less commonly, alopecia, skin fragility, and a pot-bellied appearance associated with hypercortisolism (1,2). Rarely, cats with adrenal tumors may be presented with behavioral changes secondary to excessive sex-hormone production, without concurrent hyperaldosteronism or hypercortisolism (3–5). There are several case reports in the literature describing sex hormone production in cats with adrenal tumors (3–11); however, only 2 of these cases had behavioral changes as the only clinical sign (3,4). A third case reported behavioral changes in concert with mammary hyperplasia without hyperaldosteronism or hypercortisolism (5). Differential diagnoses in these patients include retained gonadal tissue such as an ovarian remnant or retained testicle, estrogen or testosterone-producing tumors, or administration of exogenous sources of these hormones (3). Presenting with behavioral changes as the only clinical sign is atypical for cats with adrenal tumors and should be considered as a differential diagnosis in these cases.

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Case descriptions

Case 1

An 11-year-old castrated male domestic shorthair (DSH) cat (Case 1) was evaluated for behavioral changes. Six months before presentation, the cat had begun to display behavior typical of an intact male cat (mounting, urine spraying, and increased aggression toward his owners). The cat had been castrated at 4 mo of age and had never exhibited these male behaviors. Testosterone concentrations provided by the referring veterinarian before presentation at our facility were elevated at 0.37 nmol/L (reference value for a castrated male cat: ≤ 0.02 nmol/L).

On physical examination, the cat was bright, alert, and responsive but vocal, hyperactive, and difficult to handle. Spines were noted on examination of the penis (Figure 1), analogous with an intact male cat. There were no significant abnormalities on complete blood (cell) count (CBC), serum biochemistry, serum thyroxine, or urinalysis. Baseline cortisol [29.8 nmol/L; reference range (RR): 27.6 to 82.8 nmol/L] and aldosterone (382 pmol/L; RR: 194 to 388 pmol/L) concentrations were established before pursuing adrenalectomy and were within reference ranges. An anti-Müllerian hormone assay was negative for a retained cryptorchid testicle. During abdominal ultrasound, a hypoechoic left adrenal gland mass (2.5 cm × 2.4 cm × 2.2 cm) was noted with no invasion into the caudal

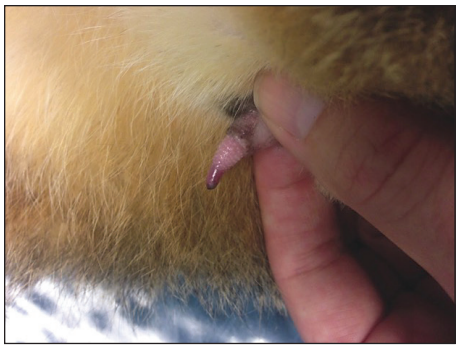

Figure 1. Penile spines present in Case 1, an 11-year-old DSH neutered at a young age.

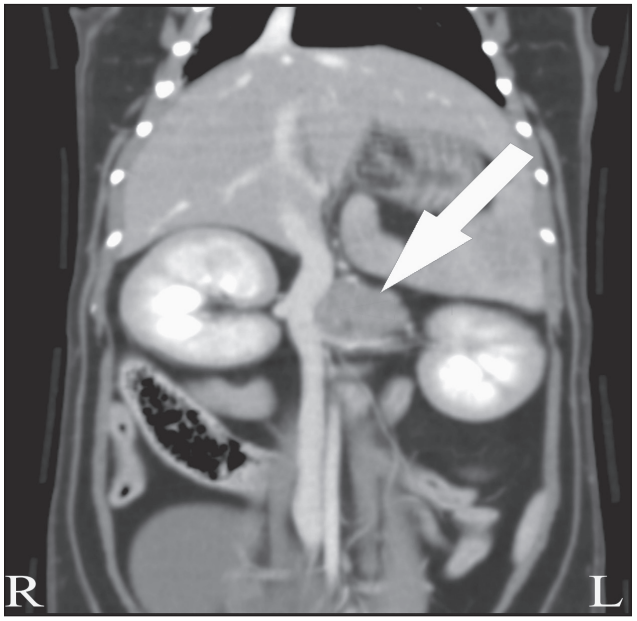

Figure 2. Preoperative CT image (post-contrast) in which a large, left-sided adrenal tumor (white arrow) is visible medial to the left kidney displacing the caudal vena cava to the right (Case 1).

vena cava. The right adrenal gland appeared normal in size and architecture and no other abnormalities within the abdomen were identified. Thoracic radiographs were unremarkable. An abdominal computed tomography (CT) scan confirmed the presence of a left-sided adrenal mass with no other significant findings (Figure 2).

The left adrenal gland and mass were removed during a standard midline laparotomy (Figure 3). The cat was administered dexamethasone (Dexamethasone sodium phosphate; Bimeda-MTC Animal Health, Cambridge, Ontario), 0.05 mg/kg body weight (BW), IV, during surgery due to the concern of a sex-hormone producing tumor potentially suppressing endogenous glucocorticoid production. Twenty-four hours after surgery the cat was hypocortisolemic (9.7 nmol/L; RR: 138 to 276 nmol/L) 1 h following administration of cosyntropin (Cortosyn; Amphastar Pharmaceuticals, Rancho Cucamonga, California, USA), 5 μg/kg BW, IV. Prednisolone (PrednisTab; Lloyd Pharmaceuticals, Shenandoa, Iowa, USA) was given for 1 mo (0.5 mg/kg BW, PO, q24h for 1 wk then 0.25 mg/kg BW, PO, q24h for 3 wk), at which point another ACTH stimulation test was performed with a baseline cortisol of 120.8 nmol/L (RR: 55 to 166 nmol/L) and post-ACTH stimulation value of 176.0 nmol/L. Prednisolone was slowly tapered with a plan to recheck in 1 mo. At recheck examination with the referring veterinarian, the baseline cortisol was 226.2 nmol/L and the post-ACTH cortisol was 268.7 nmol/L. Glucocorticoids were discontinued at that time. The cat's aggressive behavior, mounting, and urine spraying had resolved within that timeframe, 2 mo following adrenalectomy. Histopathology of the mass confirmed an adrenocortical carcinoma.

Fifteen months after surgery, the cat was presented with recurrence of virilizing behavioral signs. An abdominal computed tomography (CT) scan demonstrated apparent regrowth of the adrenal tumor with 2 closely associated, contrast-enhancing abdominal masses presumed to be metastases (Figure 4). In addition, the previously normal right adrenal gland was now a mass with extension into the caudal vena cava (Figure 4). No signs of metastasis were identified on thoracic CT. The cat was euthanized after further treatment was declined. A necropsy was not conducted.

Case 2

Case 2 was a 6-year-old neutered male cat that was presented with a 2-month history of increased aggression toward the other cat in the household, urine spraying, and weight loss. Although the cat had been neutered at 6 mo of age, spines were noted on the penis on physical examination. Testosterone concentrations were elevated at 14 nmol/L (reference value: < 0.5 nmol/L for a castrated male). An abdominal CT scan revealed a contrast-enhancing nodule on the cranial pole of the right adrenal gland measuring 9 mm $\times$ 9 mm $\times$ 7 mm; the left adrenal gland appeared normal in shape, size, and architecture. Laparoscopic surgery was performed to remove the right adrenal gland and mass. Histopathology was consistent with an adrenocortical carcinoma. Immunohistochemistry for Factor VIII-related antigen highlighted a segment of discontinuous vascular endothelium, interpreted as early vascular invasion. Testosterone concentrations taken immediately after surgery were 6 nmol/L and had fallen to 2.6 nmol/L by 2 wk post-adrenalectomy. There was resolution of behavioral signs within 5 d of surgery.

Fifteen months after surgery, the cat was seen by the referring veterinarian for weight loss and vomiting. A cranial abdominal mass was suspected on physical examination and the cat was euthanized. There had been no recurrence of behavioral signs at the time of euthanasia. A necropsy was not conducted.

Case 3

Case 3 was a 4-year-old spayed female DSH cat with a 2-month history of overt estrous behavior (pacing, vocalizing, lordosis). The cat was spayed at approximately 6 mo of age. Estradiol levels were 121 pmol/L (reference value: < 92 pmol/L for a spayed female). Abdominal ultrasound revealed a well-circumscribed 8-mm diameter mass on the right adrenal gland. The left adrenal gland appeared normal. Thoracic radiographs were normal. Under the working diagnosis of an ovarian remnant, an abdominal exploratory surgery was performed. Normal

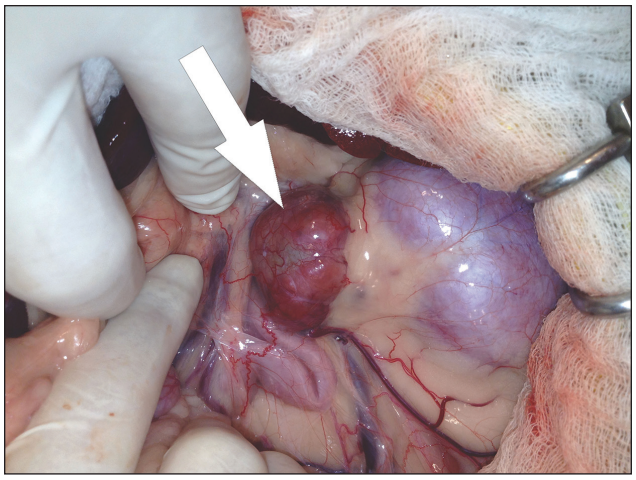

Figure 3. Intraoperative image from Case 1. A 3.3-cm left-sided adrenal tumor (white arrow) is seen medial to the left kidney. The normal right adrenal can be seen between the 2 fingers.

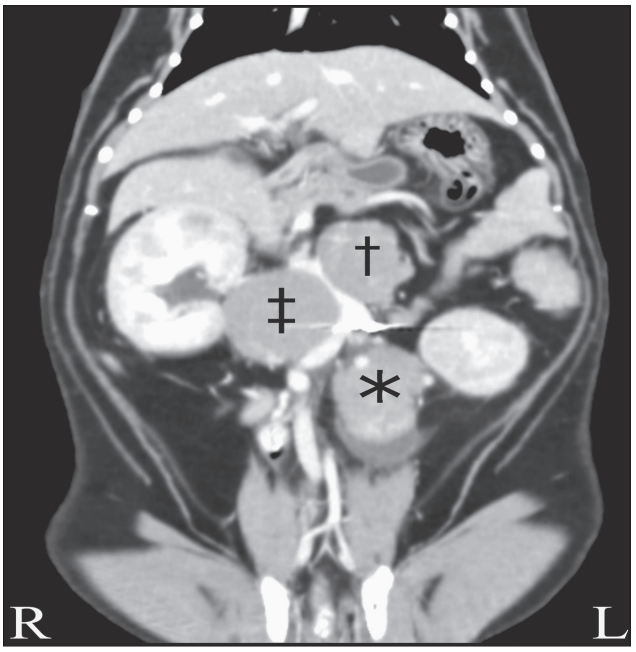

Figure 4. Computed tomographic image (post-contrast) of Case 1, 15 mo after left-sided adrenalectomy. Regrowth and metastasis of the tumor are present. There is a large mass in the region of the previously excised left adrenal gland (*). Closely associated were 2 large intra-abdominal masses presumed to be metastases. One of these lesions is visible in this view (†). In addition, the right adrenal gland is a large mass with extension into the caudal vena cava (‡).

spay scarring and adhesions were found in the region of both ovarian pedicles and a normal appearing left adrenal gland was found. The right adrenal gland and mass were removed, and histopathology of the mass was consistent with an adrenocortical adenoma. Histopathology of the spay scars was consistent with fibrosis. Clinical signs resolved within 14 d of adrenalectomy.

At 16 mo after surgery, the cat was presented for recurrence of feminizing behavioral signs. An area of irregular tissue was seen on abdominal ultrasound at the area of the previously excised right adrenal gland. Estradiol levels were once again elevated at 119 pmol/L. The cat was euthanized for presumed recurrence of the right adrenal tumor. A necropsy was not carried out.

Discussion

The clinical presentation of cats with overt sexualized behavior as the sole clinical sign secondary to an adrenal tumor is rare. Table 1 summarizes the pertinent clinical findings from the 3 cats reported here along with those cats previously reported in the literature (3–5).

Due to the few cases reported, it is difficult to draw any strong conclusions on the prognosis for cats with functional adrenal tumors causing an increase in sexually dimorphic behaviors. However, clients are particularly concerned as to whether behavioral changes are likely to resolve following adrenalectomy. All cats reported here had clinical resolution of behavioral signs within 2 mo of adrenalectomy suggesting that the prognosis is good for complete resolution of the undesirable sexual behavior following tumor removal until recurrence of the tumor.

All cats herein were euthanized within 16 mo of surgery because of recurrence of clinical signs and/or likely tumor regrowth, even though in 1 of the cats the tumor was identified as an adrenocortical adenoma. Historically, cats have been described to have a poor outcome following adrenalectomy with commonly cited reports of 4/10 cases not surviving more than 14 d after surgery and 5/8 cats dying within 5 wk (12,13). These poor outcomes appear to contrast with our findings and a more recent retrospective study of 33 cats with adrenal neoplasia (2). That study reported a median survival time following surgery of 50 wk and a 2-week survival of 77% (2). In another recent report of 11 cats undergoing laparoscopic adrenalectomy, of the 10 cats that survived to discharge, the median survival time was 114 wk (14). It appears, therefore, that the prognosis following adrenalectomy in cats may be better than previously thought. Survival times did not appear to be affected by histopathologic diagnosis of adrenocortical carcinoma or adenoma in these studies (2,12–14).

In cats with adrenal neoplasia, cortical tumors are reportedly more common than medullary tumors (91% *versus* 9%, respectively) (2). The adrenal cortex has 3 distinct layers. The outer zona glomerulosa is responsible for aldosterone secretion, the middle *zona fasciculata* largely secretes glucocorticoids but can secrete small amounts of adrenal androgens and estrogens, and the inner *zona reticularis* secretes adrenal androgens, with small amounts of estrogens, progesterone, and glucocorticoids (15,16). Tumors that originate from the *zona fasciculata* or *reticularis* could, therefore, secrete estrogen, progesterone, or testosterone resulting in behavior changes. Although the exact cortical location of the tumors reported here could not be determined by histopathology, Case 1 had plasma aldosterone and cortisol concentrations determined before surgery. The aldosterone level was within the reference range ruling out an aldosterone secreting tumor. The baseline cortisol was at the low end of the reference range, but this alone does not exclude a functional cortisol secreting tumor.

Hyperadrenocorticism in cats can be diagnostically challenging but is generally ruled out with a normal high dose dexamethasone suppression test (0.1 mg/kg BW dexamethasone IV).

Table 1. Summary of cats with adrenal tumors without hyperaldosteronism or hypercortisolaemia presenting with sexual behavior changes[a]

Case	Signalment	Presenting complaint	Duration of signs	Preoperative sex hormone levels	Tumor type	Postoperative sex hormone levels	Postoperative behavioral signs	Outcome	Survival time
1	11 y MN DSH	Urine spraying, mounting	6 mo	Testosterone 0.37 nmol/L (≤ 0.02 nmol/L castrated male). Anti-Müllerian hormone negative	Left adreno-cortical carcinoma	2 mo post-surgery: testosterone 0.03 nmol/L (≤ 0.02 nmol/L castrated male)	Complete resolution of clinical signs at 2 mo	Euthanized due to recurrence of clinical signs and presumed tumor regrowth with local metastasis	15 mo
2	6 y MN DSH	Mounting, howling, aggression, urine spraying, weight loss	2 mo	Testosterone 14 nmol/L (< 0.5 nmol/L castrated male)	Right adreno-cortical carcinoma	Immediately post-surgery testosterone 6 nmol/L (< 0.5 nmol/L castrated male). 2 wk post-surgery testosterone 2.6 nmol/L	Resolution in 5 d following surgery	Euthanized due to presumptive cranial abdominal mass	15 mo
3	4 y FS DSH	Pacing, howling, decreased appetite, agitation and rolling	2 mo	Estradiol 121 pmol/L (< 92 pmol/L spayed female)	Right adreno-cortical adenoma	N/A	Resolved within 14 d	Euthanized due to recurrence of clinical signs, elevated estradiol, irregular tissue at surgery site	16 mo
Millard et al (4)	13 y MN DSH	Urine spraying, malodorous urine, round face, weight loss	2 y	Testosterone 25 nmol/L (< 1.25 nmol/L castrated male)	Right adreno-cortical adenoma	2 wk post-surgery: testosterone 0.12 nmol/L (< 1.25 nmol/L castrated male)	Resolved by 8 wk	N/A	N/A
Meler et al (3)	15 y FS DSH	Cyclic intermittent estrous behavior (every 2 wk), posturing, licking the vulva, vocalizing, rolling on the ground and head rubbing, weight loss, aggression	1 y	Estradiol 357 pmol/L (206 to 272 pmol/L)	Right adreno-cortical carcinoma	1 mo post-surgery: estradiol 345 pmol/L (206 to 272pmol/L); 2 mo: 225 pmol/L	Resolved 24 h after surgery	Euthanized due to chronic renal failure. No evidence of tumor regrowth at that time	10 mo
Nadolksi et al (5)	14 y MN DSH	Mounting, howling, mammary hyperplasia	1 mo	Estradiol 343 pmol/L (144 to 328 pmol/L) Testosterone 0.00 nmol/L	Right adreno-cortical carcinoma	18 mo post-surgery: estradiol 210.3 pmol/L (143.5 to 327.8 pmol/L)	Resolved	600 d: no recurrence of mammary development or behavioral signs	N/A

[a] Gonadal remnants were not found in any of the cases. MN — male, neutered; FS — female, spayed; DSH — domestic shorthair; N/A — not available.

Although that test was not performed in any of the cases herein, a cortisol secreting adrenal tumor was considered unlikely as all 3 cats had normal skin and hair coats, no history of concurrent infections, and normal blood glucose levels, ruling out concurrent diabetes mellitus. Given these results, and clinical resolution of behavioral changes in all cats after surgery, it can be assumed that these tumors secreted sex hormones.

Due to the proximity of the adrenocortical layers responsible for sex hormone production and cortisol, it is important to recognize the risk of potential contralateral adrenal suppression and postoperative hypoadrenocorticism (1,2,17). In a retrospective study of cats with adrenal neoplasia, biochemical, and/or clinical hypoadrenocorticism was only identified in 3 of 26 cats after tumor removal; however, most cats were not tested for this potential postoperative complication (2). In dogs with adrenal tumors, postoperative hypoadrenocorticism is a well-recognized complication following adrenalectomy (17). It is often recommended that dogs receive dexamethasone or another glucocorticoid intravenously upon tumor removal followed by oral prednisone after surgery, tapered over approximately 3 mo (17). Similarly, electrolytes are monitored after surgery as it is possible for some abnormalities to arise within 72 h of surgery (17).

Case 1 was identified to be cortisol deficient following the administration of ACTH within 24 h of adrenalectomy. In hindsight, it would have been interesting to test glucocorticoid reserve with an ACTH stimulation test before adrenalectomy in this case, given the low normal baseline cortisol. The glucocorticoid deficiency resolved over 2 mo with glucocorticoid supplementation; however, it is important to raise awareness of this significant complication before adrenalectomy in cats. In this case, subsequent ACTH stimulation tests at 1 and 2 mo allowed initiation and completion of glucocorticoid tapering. The electrolytes remained normal throughout the peri- and post-operative periods, thus mineralocorticoid supplementation was not necessary.

In the 3 cats reported here, retained gonadal tissue was a differential diagnosis. In Case 1 this was ruled out with a negative anti-Müllerian hormone (AMH) assay. This test was recently validated in dogs and cats (18,19). In dogs, this test has a high specificity (100%) and good sensitivity (90% in females, 76% in males) for determination of remaining gonadal tissue (18). In cats, the use of an AMH assay had a 100% specificity and sensitivity in the ability to detect neuter status (19). The use of this assay is helpful in ruling out this common differential in dogs and cats. Castration status was confirmed at surgery in Cases 1 and 2, and in Case 3, visual inspection and histopathology ruled out an ovarian remnant. These findings, along with the fact that sex hormone concentrations declined and behavioral issues resolved following adrenalectomy, suggest that the behavioral changes were the result of functional adrenal tumors.

Two out of 3 cats reported here had standard midline laparotomy approaches to remove their tumors. Only 1 adrenal tumor was removed laparoscopically. A study in 48 dogs undergoing laparoscopic or open adrenalectomies found that laparoscopic procedures were associated with a low complication rate, a low conversion rate (4%), and shorter hospitalization and surgical times compared with open procedures (20). This makes laparoscopic adrenalectomy an attractive procedure for cats; however, in a previous report of 11 cats with non-invasive adrenocortical tumors removed laparoscopically, the conversion rate was 36% (14). Reasons for conversion included excessive fat, adherence to surrounding vascular structures, and inability to maintain body cavity inflation due to connective tissue fragility (14). Although minimally invasive procedures are typically associated with less postoperative pain and morbidity and increased visualization, the high conversion rate in this species needs to be recognized.

A paucity of information exists on cats presenting with an increase in sexually dimorphic behavior typically seen in sexually intact cats, as the only clinical sign secondary to an adrenal tumor. Clients are particularly interested whether behavioral changes will resolve following surgery. It appears that the prognosis for resolution of behavioral signs is good, until the mass recurs based on these 3 cats. The prognosis for survival is similar to what has been reported in recent studies. In addition, the commonly recognized complication in dogs of postoperative hypoadrenocorticism should be considered in cats and tested for and treated as necessary. For neutered cats presenting with either feminizing or virilizing behavior changes, a sex-hormone secreting adrenal tumor should be a differential diagnosis.

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