

Hyperandrogenism associated with an ovarian remnant in a spayed female cat

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Abstract

Case summary An 11-year-old female, reportedly spayed, domestic shorthair cat was examined for a 4-month history of weight loss, aggression, urine spraying, malodorous urine and estrus-like behavior. Physical examination revealed thickened skin, a mildly prominent vulva and confirmed malodorous urine. On abdominal ultrasonography, a 6 mm hypoechoic nodule was found in the left cranial abdomen. An adrenocorticotropic hormone (ACTH) stimulation test with adrenal panel revealed elevated serum concentrations of androstenedione and testosterone pre- and post-cosyntropin stimulation, mildly decreased cortisol pre- and post-cosyntropin stimulation, and decreased resting aldosterone. Exploratory laparotomy was performed and a cystic, nodular mass was found in the region of the left ovary. The mass was surgically removed and submitted for histopathology; results were conclusive for an ovarian remnant with an intact corpus luteum and non-neoplastic parovarian cysts. Previously observed clinical signs resolved within two weeks of ovariectomy. A follow-up ACTH stimulation test with adrenal panel 6 weeks postoperatively revealed normalization of serum androstenedione, testosterone and cortisol concentrations. Four years postoperatively, at the time of writing, the cat remains free of clinical signs.

Relevance and novel information We are unaware of any previously reported cases of non-neoplastic ovarian remnants associated with clinically relevant hyperandrogenism. A non-neoplastic ovarian-dependent hyperandrogenism should be included as a differential diagnosis of spayed female cats showing aggression and urine spraying behavior.

Keywords: Ovarian remnant; ovariohysterectomy; endocrinopathy; hyperandrogenism

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Case description

An 11-year-old female, reportedly spayed, domestic shorthair cat was presented for evaluation of a 4-month history of weight loss, inappropriate urination, including urine spraying, and malodorous urine. Additional clinical signs, including aggression and estrus-like behavior, were first noted 3 weeks prior to presentation. Diagnostic tests performed prior to referral included multiple urinalyses, which repeatedly revealed no significant findings. A urine culture and sensitivity had additionally been performed, which yielded no bacterial growth. Various treatment trials, including antibiotics (amoxicillin–clavulanate, enrofloxacin and cefovecin), analgesics (buprenorphine) and a prescription urinary diet (Hill’s Prescription Diet s/d Feline), were ineffective in resolving the clinical

signs. Physical examination at the time of presentation was initially limited owing to the aggressive nature of the cat. Subsequent examination under heavy sedation (dexmedetomidine and buprenorphine) revealed thickened

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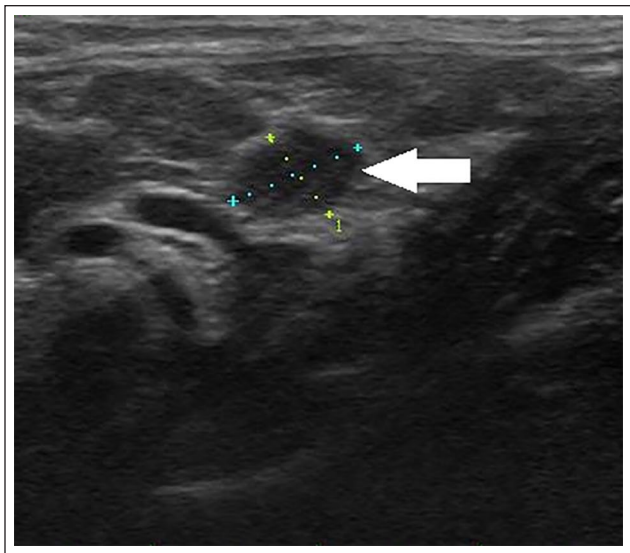


Figure 1 Ultrasonographic image of an 11-year-old spayed female domestic shorthair cat with clinical signs of aggression and urine spraying, and abnormal elevations in serum androstenedione and testosterone concentrations. A 6 mm hypoechoic nodule (white arrow) is observed in the left cranial abdomen

skin and a mildly enlarged vulva, but no other abnormalities were detected.

A complete blood count and serum chemistry panel were performed, and the results were within normal limits. Abdominal ultrasonography revealed a 6 mm hypoechoic nodule in the left cranial abdomen (Figure 1); the adrenal glands were not well visualized, but no other abnormalities were identified. An adrenocorticotropic hormone (ACTH) stimulation test with complete adrenal panel was performed at the Diagnostic Endocrinology Service, University of Tennessee College of Veterinary Medicine (Table 1), in which elevated serum concentrations of androstenedione and testosterone pre- and post-cosyntropin stimulation, mildly decreased cortisol pre- and post-cosyntropin stimulation, and decreased resting aldosterone were observed. These results were consistent with hyperandrogenism.

The cat was placed under general anesthesia (pre-medication: hydromorphone and midazolam; induction: propofol; maintenance: isoflurane) and a routine ventral midline exploratory laparotomy was performed. A nodular mass was observed in the region of the left ovary (Figure 2). Both adrenal glands were normal in size and appearance. The nodular mass was removed by ligating the blood supply with hemoclips and excising the structure. Abdominal closure was routine. The cat made an uneventful recovery from anesthesia and was discharged from the hospital the following day. Histopathology confirmed the diagnosis of an ovarian remnant that appeared completely excised. Within the ovary, a nodule composed of round cells with abundant lipid-type cytoplasmic vacuoles was observed, consistent with an intact corpus luteum. Non-neoplastic parovarian cysts were also observed. No definitive cause of the elevated testosterone and androstenedione was apparent.

On follow-up examination, complete resolution of clinical signs was apparent within 2 weeks of surgery. An ACTH stimulation test with complete adrenal panel was repeated at 6 weeks post-ovariectomy (Table 2), which revealed normalization of serum testosterone, androstenedione and cortisol concentrations. The owner was contacted by telephone for follow-up 4 years after ovarian remnant removal. The cat was reportedly doing well at home, with no recurrence of urine spraying or unusual aggression. The owner reported that the cat had returned to normal behavior patterns and body condition shortly after surgery.

Discussion

The cat in the present report had clinical signs and endocrinologic findings consistent with hyperandrogenism. Several reports of sex hormone-secreting adrenocortical tumors have been described in cats.¹⁻⁷ Many of these cases involved overproduction of one or more of the following hormones: progesterone, aldosterone, estradiol, testosterone and androstenedione. One case report describes a neutered male cat that had clinically relevant elevations in androstenedione and

Table 1 Results of adrenocorticotropic hormone (ACTH) stimulation test with complete adrenal panel at presentation

Test	Result (baseline)	Reference interval*	Result (1 h post-ACTH)	Reference interval*
Cortisol (ng/ml)	5.0 [†]	5.2–54.4	26.5 [†]	52.8–150
Androstenedione (ng/ml)	0.91 [†]	0.1–0.3	2.30 [†]	0.4–2.0
Estradiol (pg/ml)	76.0	50.3–84.0	74.2	41.8–79.7
Progesterone (ng/ml)	0.20	0.03–0.4	0.89	0.5–5.2
17-OH progesterone (ng/ml)	0.08	0.08–0.2	0.45	0.2–1.6
Aldosterone (pg/ml)	<11.0 [†]	11.3–294.3	16.2	No values
Testosterone (ng/ml)	2.24 [†]	0.02–0.3	5.15 [†]	0.02–0.4

*Reference intervals (RIs) for spayed female cats

[†]Above or below RI

17-OH progesterone = 17-hydroxyprogesterone

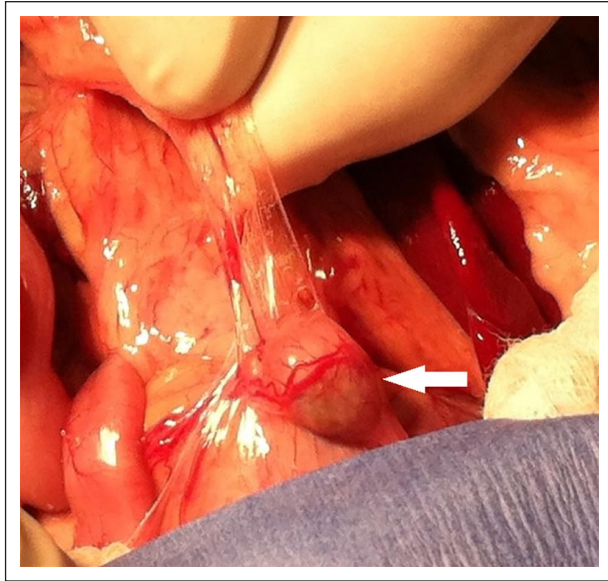


Figure 2 Intraoperative photograph during exploratory laparotomy of the cat in Figure 1. A left-sided ovarian remnant (white arrow) was found and excised

testosterone, which resolved within 2 weeks of surgical excision of an adrenocortical adenoma.⁴ In the present case report, a functional adrenocortical tumor secreting excess androgens was originally suspected owing to the altered reproductive status of the cat and the initial interpretation of the ultrasonographic findings. However, at the time of surgery, the adrenals were grossly normal in size and appearance, and an ovarian remnant was found. Given the resolution of clinical signs and normalization of testosterone and androstenedione post-ovariectomy, this case represents an ovarian-dependent hyperandrogenism.

In the present case, an ovarian remnant was associated with excessive androgens and resolved with its excision. Ovarian remnant syndrome (ORS) is a condition in which functional ovarian tissue is present in a reportedly

ovariectomized animal.^{8–10} While reports exist regarding the potential for excised ovarian tissue to become revascularized and functional,⁸ the majority of retrospective studies support an etiology of surgical error owing to the recovery of ovarian remnants in typical anatomical locations.^{9,10} In cats diagnosed with ORS, behavioral and clinical signs are often consistent with estrus owing to the presence of circulating estrogen, including vocalization, lordosis and attraction of tom cats.^{9,10}

Residual ovarian tissue can also undergo neoplastic transformation. In one study, 24% of dogs and cats treated for ORS were diagnosed with ovarian neoplasms on histopathology, with sex cord stromal tumors being the most common.¹⁰ This category of tumors – including thecomas, luteomas and granulosa cell tumors – are the most common primary ovarian neoplasm in cats.¹¹ These tumors commonly secrete estrogen, androgens or both, and can cause hormonal disturbances leading to abnormal estrus and behavior.¹² In this case, no neoplastic tissue was observed histologically to account for the abnormal hormone secretion. While non-neoplastic, ovarian-dependent hyperandrogenism has been reported in other species such as cattle,¹³ and also in women,^{14,15} to our knowledge this is the first reported case confirmed in a cat.

No cause for the hyperandrogenism was readily evident on histologic examination of the excised ovarian remnant. The normal morphology of the ovary can be obscured in ORS;¹⁶ therefore, it is possible that diagnostic histologic features were not apparent in this case. For example, the reported parovarian cysts may have represented cystic rete ovarii, which have been known to secrete hormones in cats, though the clinical significance of this is currently unknown.¹⁷ Alternatively, ectopic adrenocortical tissue located in the broad ligament of cats has been reported, and would be another potential cause of excess sex hormone production in this case.¹⁸ Other possible mechanisms for ovarian-dependent, non-neoplastic hyperandrogenism in this case could include aberrant biosynthetic pathways or enzyme deficiencies in steroidogenesis, as has been

Table 2 Results of adrenocorticotrophic hormone (ACTH) stimulation test with complete adrenal panel 6 weeks post-ovariectomy

Test	Result (baseline)	Reference interval*	Result (1 hour post-ACTH)	Reference interval*
Cortisol (ng/ml)	38.4	5.2–54.4	74.7	52.8–150
Androstenedione (ng/ml)	<0.1 [†]	0.1–0.3	1.31	0.4–2.0
Estradiol (pg/ml)	62.0	50.3–84.0	57.5	41.8–79.7
Progesterone (ng/ml)	0.17	0.03–0.4	2.10	0.5–5.2
17-OH progesterone (ng/ml)	0.14	0.08–0.2	0.95	0.2–1.6
Aldosterone (pg/ml)	<11.0 [†]	11.3–294.3	102.8	No values
Testosterone (ng/ml)	0.01	0.02–0.3	0.01	0.02–0.4

*Reference intervals (RIs) for spayed female cats

[†]Above or below RI

17-OH progesterone = 17-hydroxyprogesterone

postulated in women with polycystic ovary syndrome¹⁹ and for functional adrenal tumors.⁴

Histopathology of the ovarian remnant in this cat revealed a corpus luteum (CL). However, serum progesterone levels were low, indicating that the CL was non-functional. Although not identified in the histopathology of the retained ovary in this case, ectopic adrenal tissue has been reported in the ovary in humans.²⁰ If ectopic adrenal tissue had been found in the present cat it would offer a convenient explanation of the source of androgens and resultant clinical signs.

Conclusions

We are not aware of any previously reported non-neoplastic ovarian remnant-associated hyperandrogenism in cats. This disorder should be considered as a differential diagnosis in reportedly spayed female cats exhibiting behavioral changes, especially androgen-mediated behavior. Evaluation (ultrasonographic and endocrinologic) and intervention via exploratory celiotomy or laparoscopy should be curative in these cats. Further study of steroidogenesis is warranted to investigate functional ovarian hyperandrogenism in cats.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval This work involved the use of non-experimental animals only (owned or unowned), and followed internationally recognized high standards ('best practice') of individual veterinary clinical patient care. Ethical approval from a committee was not necessarily required.

Informed consent Informed consent (verbal and written) was obtained from the owner or legal guardian of the animal described in this work for the procedure undertaken. No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

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