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CASE REPORT

Companion or pet animals

Hyperprogesteronism associated with adrenocortical tumours in two dogs

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Abstract

A 9-year-old, entire, female, soft-coated Wheaten terrier and a 7-year-old, male, neutered greyhound were presented for clinical signs suggestive of hyperadrenocorticism (polyuria, polydipsia, and in the first case, polyphagia and weight gain). Adrenocorticotrophic hormone stimulation test and low-dose dexamethasone suppression test ruled out excessive production of cortisol. Imaging (abdominal ultrasound and computed tomography) revealed an adrenal mass in both cases. Further hormonal testing revealed hyperprogesteronism. In the first case, surgical treatment was not considered due to vascular invasion of the mass, the patient was treated successfully with trilostane and was still stable 18 months later. In the second case, adrenalectomy was performed, and the clinical signs resolved, the dog was stable 10 months later. We report two clinical cases of progesterone-secreting adrenocortical tumours and their management.

KEYWORDS

hyperadrenocorticism, surgery, trilostane

BACKGROUND

Adrenal masses and nodules are relatively rare in dogs and have been found in 4%–9% of dogs undergoing abdominal imaging.[1,2] Most adrenal tumours are adenomas or adenocarcinomas and secrete cortisol.[3] Pheochromocytomas are tumours from the adrenal medulla and secrete catecholamines.[4] Although rare, other adrenocortical tumours described in the dog are aldosterone-secreting and sex-hormone-secreting tumours.[5,6] Only two dogs have been described with functional adrenocortical tumours that were associated with overproduction of multiple sex hormones and presented with clinical signs compatible with hyperadrenocorticism (or Cushing's disease).[5]

This report describes two adrenocortical tumours associated with clinical signs of hypercortisolism, but which were associated with increased concentrations of progesterone. In contrast to the previous report,[5] other sex hormones were not increased.

CASE PRESENTATION

Case 1

A 9-year-old, entire, female soft-coated Wheaten terrier weighing 17.4 kg was presented with polyuria, polydipsia, polyphagia and weight gain. Its owners also reported delayed oestrus (the last reported oestrus was 13 months ago). On clinical exam, it was found to be normothermic, bright, alert and responsive. It had a pot-bellied appearance, but no signs of alopecia (Figure 1). It was slightly tachycardic (136 beats per

FIGURE 1 Case 1 at presentation showing mild pot-bellied appearance, but no alopecia.

minute), but appeared very stressed and panting, so this is not thought to be significant, pulse rate and rhythm were strong and regular. There were no other abnormalities on physical examination.

An adrenocorticotrophic hormone (ACTH) stimulation test and a low-dose dexamethasone suppression test had already been performed by the referring practice. The ACTH stimulation test was consistent with hypocortisolism (pre-ACTH cortisol was 11.1 nmol/L, post-ACTH cortisol was 42.5 nmol/L). The low-dose dexamethasone suppression test results were 16.4, 9.3 and 7.9 nmol/L at 0, 3 and 8 hours post dexamethasone administration, respectively, not consistent with hyperadrenocorticism.

LEARNING POINTS/TAKE-HOME MESSAGES

- In the presence of an adrenal tumour and clinical signs but with negative tests for hypercortisolism, excess progesterone should be considered.
- The diagnosis of a progesterone-secreting adrenocortical tumour requires determination of progesterone concentration in the context of an adrenocorticotrophic hormone stimulation test.
- Treatment with trilostane may be considered for progesterone-secreting adrenocortical tumours when surgery is not possible.

Case 2

A 7-year-old, male, neutered greyhound weighing 34.2 kg was presented with a 5-month history of polyuria and polydipsia, and progressive lethargy. There were no changes in appetite or coat appearance reported. Previous bloodwork (haematology and biochemistry) and imaging (abdominal ultrasound) performed at the referring vets had revealed no significant abnormalities. Urinalysis had revealed a moderately dilute urine (specific gravity was 1.016) and the presence of protein on the dipstick. The patient had received two courses of co-amoxiclav for suspected urinary tract infection, without improvement.

On physical examination, the patient was normothermic, bright, alert and responsive and in good bodily condition (scored at 5/9). Tachycardia (136 beats per minute) and panting, suspected to be stress related, were noted, but there were no abnormal sounds on thoracic auscultation. Marked dental disease was noted. There were no other abnormalities on clinical examination, including a retinal examination.

INVESTIGATIONS

Case 1

Routine biochemistry (Table 1) showed increases in alanine transferase at 158 iu/L (reference range: 0–90 iu/L) and cholesterol at 9.53 mmol/L (reference range: 2–7 mmol/L). Phosphate was reduced at 1.03 mmol/L (reference range: 1.29–2.9 mmol/L). A lymphopenia was seen on haematology at 0.724×10^9/L (reference range: 1–4.8×10^9/L). These changes, though all mild, were consistent with hypercortisolism. Blood pressure was mildly increased with a systolic blood pressure of 157 mmHg.

Abdominal ultrasonography identified a large right adrenal mass (65 × 43 mm). There was the suspicion that it was locally infiltrating the vena cava with local lymphadenopathy. The left adrenal gland was of normal size (4.7 mm) and echotexture. Some focal changes were seen in the caudate liver lobe, but were non-specific and a round hyper-echoic nodule was also seen in the left central aspect of the liver (which could represent focal nodular hyperplasia, metastatic neoplasia or a granuloma). Radiographs of the thorax (left and right lateral and dorsoventral) and abdomen (R lateral) showed no obvious signs of metastasis.

An ACTH stimulation test was performed. The results are shown in Table 2. The cortisol results were suggestive of hypocortisolism. Electrolytes were within reference range (Table 1), and the dog was not significantly hypertensive, which was not suggestive of hyperaldosteronism. Therefore, aldosterone was not measured.

A panel of sex hormones was requested. The results suggested hyperprogesteronism. The urine cortisol:creatinine ratio was 34 (reference range: 0–30). A urine normetanephrine:creatinine ratio was measured in acidified frozen urine. The result was not consistent with a phaeochromocytoma. The endogenous ACTH was undetectable, suggesting steroid suppression of pituitary ACTH production. A progesterone-secreting tumour was therefore considered the most likely cause of the hyperprogesteronism.

To investigate the possibility of surgery (adrenalectomy with venotomy), contrast-enhanced computed tomography (CT) was performed. A bilobed right adrenal mass (65 mm long, 47 mm high and 52 mm wide) was seen (Figure 2). It was generally homogeneous, soft tissue attenuating (37 HU) and mainly non-contrast enhancing. At its medial aspect, the mass extended into the prehepatic caudal vena cava. The defect in the wall of the caudal vena cava was estimated to be approximately 1.5 cm long and was located just cranial to the right renal vein. The length of tumour within the caudal vena cava was approximately 2 cm. Within this region, the mass occupied up to half of the cross-sectional area of the caudal vena cava, reducing the lumen of the caudal vena cava to a crescent shape. Beyond this extension into the caudal vena cava, the mass also extended to the left of midline and was in contact with the left adrenal gland. The ventral part of the mass was displacing the right kidney and indenting it. Caudally, the mass displaced the right renal vein and right renal artery.

The mass was seen in the arterial phase to have a large collection of arteries (some within the mass, some inside the caudal vena cava) and also had three mineral foci, two of which were themselves within the caudal vena cava. In contrast to the abdominal ultrasound, the abdominal lymph nodes, including the renal/aortic and medial iliac lymph nodes, were regarded as normal. There was also a small lesion noted in the lung, but this was thought to be incidental and not a metastasis.

TABLE 1 Haematology, biochemistry and urinalysis results at presentation from the two cases.

Test	Results Case 1	Results Case 2	Reference range
Biochemistry			
Sodium (mmol/L)	145.1	153.0	136–159
Potassium (mmol/L)	3.4	5.56	3.4–5.8
Chloride (mmol/L)	109.6	108.2	95–115
Calcium (mmol/L)	2.41	2.36	2.34–3
Phosphate (mmol/L)	L 1.03	L 0.7	1.29–2.9
Urea (mmol/L)	2.7	5.3	2.5–8.5
Creatinine (μmol/L)	54	H 162	45–155
Glucose (mmol/L)	5.2	4.9	3–5.5
Cholesterol (mmol/L)	H 9.53	5.88	2–7
Triglyceride (mmol/L)	0.6	H 0.79	0–0.6
Total bilirubin (μmol/L)	3	4	0–10
Alkaline phosphatase (U/L)	59	41	0–230
Aspartate aminotransferase (U/L)	19	31	0–40
Alanine transferase (U/L)	H 158	53	0–90
Gamma-glutamyl transferase (U/L)	14	13	0–20
Total protein (g/L)	62	62	50–78
Albumin (g/L)	33	32	29–36
Globulin (g/L)	29	30	28–42
Haematology			
Red blood cells (×10 E12/L)	6.9	8.05	5.5–8.5
Haemoglobin (g/dL)	16.6	H 21.9	12–18
Hematocrit (%)	47.4	H 0.606	37–55
White blood cells (×10 E9/L)	9.05	7.3	6–12
Band neutrophils (×10 E9/L)	0.09	0	0–0
Neutrophils (×10 E9/L)	8.145	4.32	3–11.8
Lymphocytes (×10 E9/L)	L 0.724	1.99	1–4.8
Monocytes (×10 E9/L)	L 0.09	0.58	0.15–1.35
Eosinophils (×10 E9/L)	0	0.39	0.1–1.25
Basophils (×10 E9/L)	0	0.02	0–0
Platelets (×10 E9/L)	262	206	200–500
Urinalysis			
Urine specific gravity	1.030	1.004	
pH (urine)	6	8	
Qualitative protein	+++VE	++VE	
Qualitative blood	−VE	++VE	
Qualitative glucose	−VE	−VE	
Qualitative ketones	−VE	−VE	
Protein:creatinine ratio	N/A	3.01	
Sediment	N/A	Unremarkable	

Case 2

Routine biochemistry (Table 1) was repeated, and a mildly increased creatinine at 162 μmol/L (reference range: 45–155 μmol/L) was noted. Creatinine has been reported to be higher in greyhounds than in other breeds,[7] and the patient had a normal urea at 5.3 mmol/L (reference range: 2.5–8.5 mmol/L) and normal symmetric dimethylarginine (previously measured by the referring vets) at 15 μg/dL (reference range: 0–20 μg/dL), therefore kidney disease was considered unlikely to be the cause of its polyuria-polydipsia. Phosphate was decreased at 0.7 mmol/L (reference range: 1.29–2.9 mmol/L), although it has been reported to be lower in greyhounds than in other breeds.[7] Triglyceride was mildly increased at 0.79 mmol/L (reference range: 0–0.6 mmol/L). Ionised calcium, liver enzymes and electrolytes were normal.

Abdominal ultrasonography identified a rounded heterogeneous mass (20 mm) to the cranial pole of the left adrenal gland. The right adrenal gland was normal in size (7 mm)

TABLE 2 The endocrine results at presentation from the two cases.

	Pre ACTH			Post ACTH		
Case	**Case 1**	**Case 2**	**Reference range[a]**	**Case 1**	**Case 2**	**Reference range[a]**
Sex	FE	MN		FE	MN	
Cortisol (nmol/L)	10	16.8	0–250[b]	40.6	168	80–450[b]
Oestradiol (pmol/L)	8.1	<5	(0–10)[b,c]	<5	<5	
Progesterone (nmol/L) (radioimmunoassay)	5.2	2	Anoestrous < 3.0 Metoestrus > 48[b] Males < 0.95[d]	>200	16	Female entire < 11.8 Male neutered < 6[d]
17-Hydroxyprogesterone (nmol/L)	<0.3	0.43	0–0.3[b]	2.1	2.15	3.0–8.0[b]
Androstenedione (nmol/L)	0.28	0.37	(0–2.4), (0–0.8)[b]	0.92	<0.3	
Testosterone (nmol/L)	0.16	0.12	Female entire < 1 Male neutered < 0.35[d]	0.52	0.16	Female entire < 1.4 Male neutered < 2.4[d]
Endogenous ACTH (pg/mL)	<5	7	13–46[b]			
Urine normetanephrine:creatinine ratio (radioimmunoassay)	55	61	<100[b]			

Abbreviation: ACTH, adrenocorticotrophic hormone.
[a]Entire female, neutered male shown where different.
[b]Reference range from laboratory.
[c]>10 indicated follicular activity in the female, Sertoli tumours in the male.
[d]Reference range from published sources.[28]

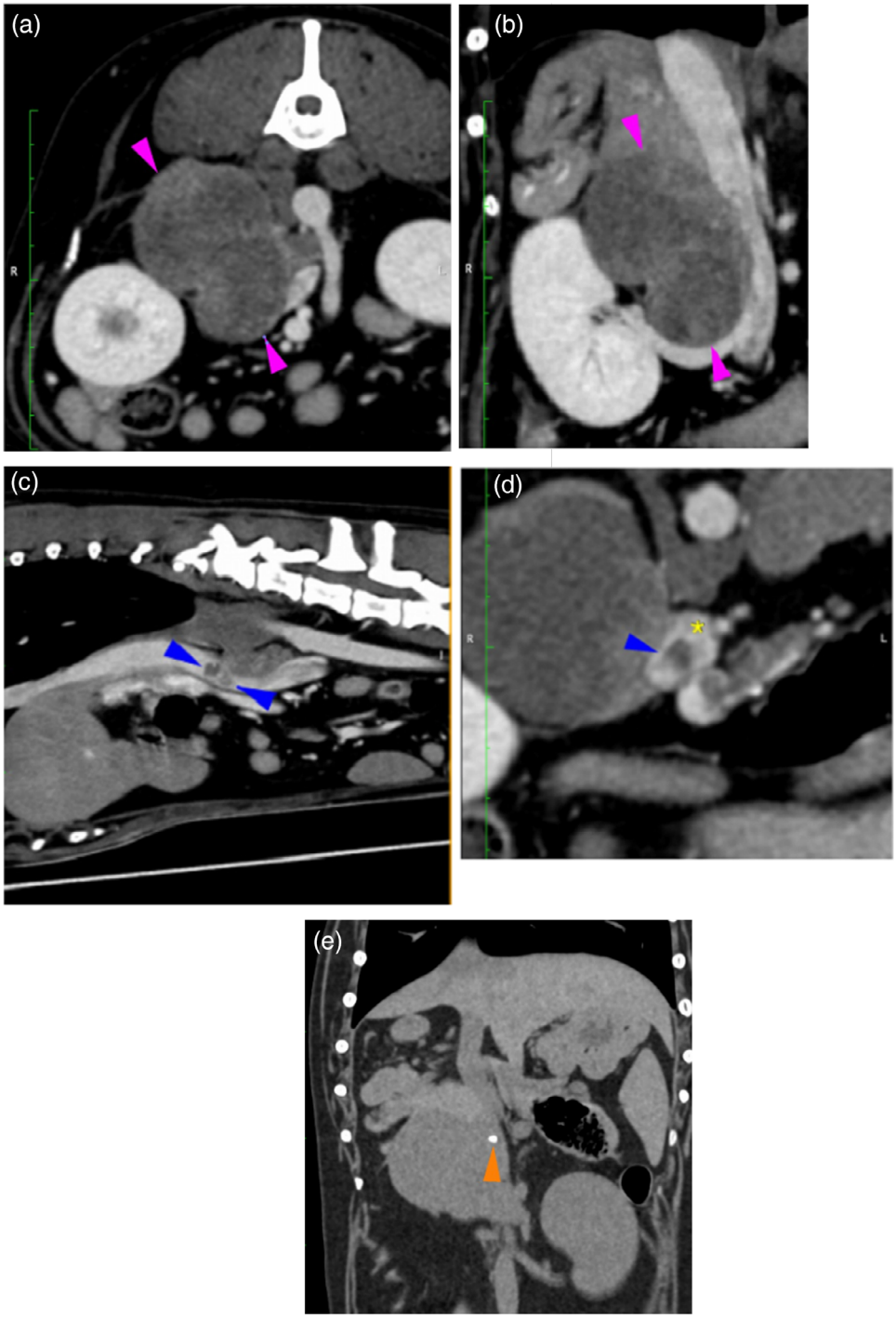

FIGURE 2 Contrast-enhanced computed tomography of Case 1 showing (A) bilobed adrenal tumour (pink arrows), (B) extensive contact between the tumour and the caudal vena cava with filling defects in the latter. (C) Filling defects within the caudal cava (blue arrows) in longitudinal section, and (D) the reduction in the lumen of the caudal vena cava to a crescent shape (yellow asterisk). (E) On its medial aspect, the mass extended to the left of midline with area of calcification (orange arrowhead), ventral to the aorta and was in contact with the left adrenal gland.

and echogenicity. The pancreas was hypoechoic and surrounded by echogenic mesenteric fat, consistent with mild pancreatitis. The liver was homogeneously hypoechoic with increased portal markings. Multiple small gall bladder polyps were seen, of unknown clinical significance. The urinary tract was normal in appearance, and a urine sample was obtained by cystocentesis. Urinalysis showed hyposthenuric urine (urine specific gravity [USG] = 1.004). Moderate proteinuria was noted (urine protein to creatinine ratio = 3.01). Urine sediment was inactive. There was no bacterial growth when the sample was cultured. In-house urinalysis on a free-catch sample obtained later that day showed isosthenuric urine (USG = 1.012). Blood pressure was normal at 122/87 mmHg, with a mean arterial pressure of 96 mmHg.

Further investigations of the adrenal mass were performed to determine if it was functional. A low-dose dexamethasone suppression test showed suppression and was not supportive of a diagnosis of hypercortisolism (resting cortisol was 57.7, 13.7 and 11.1 nmol/L at 0, 3 and 8 hours post dexamethasone, respectively). An ACTH stimulation test was also not

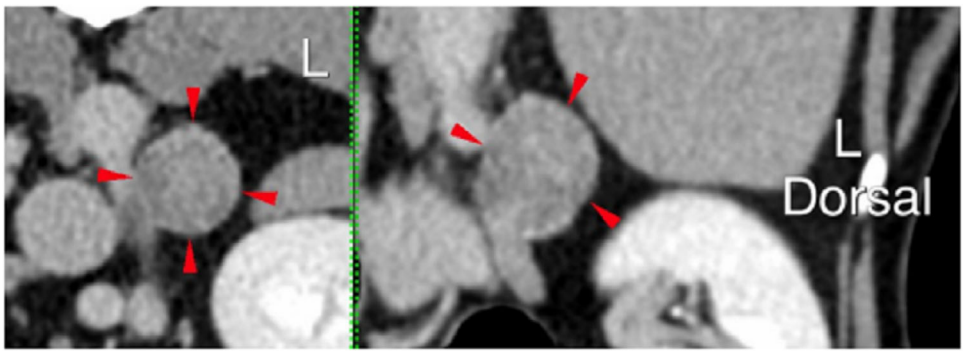

FIGURE 3 Contrast-enhanced computed tomography of Case 2 showing the tumour in this case (red arrows).

supportive of a diagnosis of hypercortisolism or hypocortisolism (Table 2). Endogenous ACTH was decreased, suggesting a degree of negative feedback on the pituitary–adrenal axis. The urine normetanephrine:creatinine ratio was not considered as supportive of a diagnosis of pheochromocytoma. Urine cortisol:creatinine ratio was not measured. Aldosterone was not measured, as the dog's electrolytes and blood pressure were normal.

A panel of sex hormones (progesterone, oestradiol, testosterone, androstenedione and 17-OH-progesterone) was measured in this case in order to ascertain if they could be the cause of the low endogenous ACTH (Table 2). The basal progesterone and post-ACTH progesterone were both increased compared to what would be normal in a neutered male dog. Oestradiol, testosterone, androstenedione and 17-OH-progesterone were normal pre-ACTH. Post-ACTH concentrations of 17-OH-progesterone were below the laboratory's reference range. Post-ACTH concentrations of the other hormones were normal.

Abdominal CT scan with contrast showed a well-defined, oval, smooth, soft tissue attenuating, heterogeneously contrast-enhancing mass within the cranial pole of the left adrenal gland (Figure 3, red arrows) that measured 28 mm craniocaudal × 22 mm mediolateral × 22 mm dorsoventral. There was no enlargement or vascular filling defects identified within the left phrenicoabdominal vein or caudal vena cava. The caudal pole of the left adrenal gland and right adrenal gland were within normal limits (7 mm). The other abdominal organs were within normal limits. Thoracic CT scan showed a well-defined, smooth, fusiform, homogenously fluid attenuating nodule within the cranial mediastinum, ventral to the trachea and dorsal to the cranial vena cava and brachycephalic arterial trunk. This was most likely benign (a branchial cyst or a cystic cranial mediastinal lymph node), with a neoplastic aetiology considered much less likely. No pulmonary metastases were seen.

TREATMENT

Case 1

After discussion of the relative risks of surgery and medical management, the owner opted for trilostane (Vetoryl; Dechra Pharmaceuticals), and a dose of 10 mg every 12 hours by mouth (equivalent to 0.6 mg/kg every 12 hours) was prescribed. Two days later, the dog was reported to be unwell and occasionally collapsing with some vomiting. On clinical examination, it was found to be reasonably bright, and its electrolytes were normal, with sodium being 151 mmol/L (reference range: 144–160) and potassium was 3.4 mmol/L (reference range: 3.5–5.8). Abdominal ultrasonography demonstrated free abdominal fluid, which on abdominocentesis was found to be blood. Intravenous fluids were provided, and the dog responded well and was discharged (as the owner did not wish any further investigations). Trilostane was continued.

Case 2

The patient underwent left adrenalectomy under general anaesthesia. In dorsal recumbency, a xyphoid-umbilical midline celiotomy was performed, and a nodule at the cranial pole of the left adrenal gland was identified. After meticulous dissection on medial aspect of the left adrenal gland and haemostasis around this gland, a left adrenalectomy was completely performed without intraoperative complications. Lavage of the left adrenal area was performed with warm sterile saline, followed by omentalisation of the area. Celiotomy closure was performed routinely. The left adrenal gland was submitted to histopathological analysis.

The surgery and postoperative period were without significant complications. The patient's electrolytes were monitored daily and remained normal. Forty-eight hours after surgery, it was noted to be hypertensive with systolic arterial blood pressure persistently greater than 200 mmHg, but this resolved without treatment. No treatment with glucocorticoids was felt to be necessary. The patient was discharged 4 days after surgery.

OUTCOME AND FOLLOW-UP

Case 1

The dog was presented 2 months later. The dog was reported to be doing well on treatment, with improvements in activity levels and hair coat. The thirst, urination and appetite were all now considered to be normal. On clinical examination, the hair coat was still a little thinner dorsally, some seborrhoea sica was present on its ventrum and the dorsal aspect of its neck,

but overall there was considerable improvement. There were no other significant findings.

As treatment of hyperprogesteronism had not been described before, it was considered important to assess the best method of monitoring the patient going forward. To this end, the dog was admitted for a pre-pill, post-pill and post-ACTH progesterone, together with a post-ACTH cortisol.[8] After the initial blood sample, the dog was given 10 mg trilostane with food, and an ACTH stimulation test was performed 3 hours later.

The pre-pill progesterone was 2.1 nmol/L (having been 5.2 nmol/L previously), the post-pill/pre-ACTH progesterone result was 1.5 nmol/L. The post-ACTH progesterone was 3.8 nmol/L (having been over 200 nmol/L before diagnosis). The post-ACTH cortisol was 32 nmol/L. The cortisol result was lower than normally advised, but as the dog was very lively and well, it was decided to continue the current dose. However, the owner was advised that should the dog show signs of lethargy and poor appetite, then prednisolone should be given and the trilostane dose reduced to 5 mg twice daily.

Two months later, the dog came into season normally (consistent with adequate suppression of progesterone).

The dog was seen by its original veterinary surgeon 6 months later (and 8 months after original diagnosis). An ACTH stimulation test was performed 3 hours after trilostane administration. The progesterone results were considered satisfactory (pre-ACTH progesterone was 7.6 nmol/L; post-ACTH progesterone was 14 nmol/L), as they were markedly decreased compared to the values before treatment and close to normal (see Table 2 for reference range). No biochemistry, urinalysis or ACTH assay were repeated.

The dog was reported to be continuing to do well 18 months post diagnosis and was still receiving trilostane.

Case 2

Histopathology of the left adrenal gland showed that the normal architecture was distorted by a nodular, relatively well-demarcated but occasionally slightly invasive mass, which appeared to be arising from the cortex. The mass consisted of trabeculae and lobules of cells with scant fibrovascular stroma. The cells were polygonal with large amounts of finely granular to finely vacuolated amphophilic cytoplasm. The nuclei were round to ovoid with dispersed chromatin and single prominent nucleoli. Cell and nuclear size variation was moderate. Mitotic figures were present at a rate of one per 10 high power (400×) fields. Vascular invasion was not definitively observed, and the tumour appeared to be completely confined within the capsule of the adrenal gland. These findings were most likely consistent with an adrenocortical adenocarcinoma.

One week after surgery, the owner reported that the patient was still polyuric and polydipsic, but to a lesser extent than before surgery. Two weeks after surgery, the owner reported that its drinking and urination were back to normal levels.

The dog was reassessed 6 months after surgery. Its owners reported normal energy levels and no polyuria or polydipsia (specific gravity of 1.037). Basal progesterone was 0.5 nmol/L, cortisol was 42 nmol/L and post-ACTH progesterone was 3.5 nmol/L, with cortisol being 220 nmol/L. These results were consistent with normal secretion of progesterone.

Ten months after surgery, the dog was still reported to be doing well, with no recurrence of polyuria and polydipsia.

DISCUSSION

These are the first case reports of progesterone-secreting adrenocortical tumours in dogs. Both cases had clinical signs and changes on routine blood tests that were thought to be compatible with hypercortisolism. However, endocrine testing in both cases failed to confirm oversecretion of cortisol, and in one case the cortisol secretion appeared to be so low that it would have been consistent with hypoadrenocorticism. In neither case were mammary development or behaviour signs seen.

Hyperprogesteronemia has previously been reported in a bitch with ovarian luteoma,[9] and in women with ovarian Sertoli cell tumour,[10] granulosa cell tumour[11] and Leydig cell tumour.[12] In Case 1, we did not investigate a potential ovarian origin to the excessive production of progesterone, as no ovarian abnormalities were found on imaging. In human medicine, adrenal and ovarian venous sampling has been described to differentiate adrenal from ovarian production of progesterone.[13]

In women, hyperprogesteronemia usually causes amenorrhea[13–17]; the dog in Case 1 also had delayed oestrus (13 months, when its owners reported that it previously had regular oestrus every 6 months). The effect of progesterone on the mood and behaviour is not clear.[18]

In the first case, the urine cortisol:creatinine ratio was higher than would be expected in a normal dog and also in a dog with low plasma cortisol secondary to a progesterone-secreting tumour. However, the radioimmunoassay used is known to show significant cross reactivity with corticoid metabolites, and it is possible that progesterone metabolites may also be recognised.[19]

Contralateral adrenal glands were normal in size in the two cases described in this report. Some cats with aldosterone- and progesterone-secreting adrenocortical tumours have been described to have a normal-size contralateral adrenal gland, although the cats with low plasma cortisol had small contralateral adrenals.[20] A normal-size adrenal in Case 1 is a surprising finding in the context of low plasma cortisol.

Three of the 10 cats with aldosterone- and progesterone-secreting adrenocortical tumours had increased concentrations of corticosterone that could have participated in the hypothalamic–pituitary–adrenal axis suppression.[20] Corticosterone has glucocorticoid effect through binding of glucocorticoid receptors.[21] An adrenocortical tumour secreting aldosterone and corticosterone and causing clinical signs of hyperadrenocorticism has been reported in a dog.[6] Corticosterone was not measured in the two cases presented in this report; this represents a limitation to this report.

Hyperprogesteronemia caused polyuria and polydipsia and other signs of Cushing's syndrome in the two cases reported here. Progesterone and synthetic progestogens are known to cross-react with the glucocorticoid receptor, and when present in excessive quantities are likely to produce Cushing's syndrome.[21] This also explains why signs of hypocortisolism were not present in Case 1 despite cortisol results that were consistent with hypoadrenocorticism.

Both cases were managed successfully; one with surgery, the other with trilostane. Trilostane as a cortisol synthesis inhibitor would also appear to have some action on the synthesis of progesterone in the adrenal glands of dogs. This has been suspected from in vitro studies; however, there is some disagreement as to the effect on progesterone synthesis in corpora lutea.[22,23]

Previous reports of functional but non-cortisol-producing adrenocortical tumours in dogs are confined to cases where multiple endocrine abnormalities were detected. Syme et al. previously described two dogs with clinical signs compatible with hyperadrenocorticism and adrenocortical tumours secreting multiple sex hormones. Cortisol testing did not support a diagnosis of hypercortisolism in either dog; however, imaging studies revealed unilateral adrenal tumours in both dogs. Serum concentrations of 17-hydroxyprogesterone, progesterone and oestradiol were high in both dogs, and androstenedione concentrations were also high in one dog. Clinical signs and hormonal abnormalities resolved in the male dog after surgical resection of the tumour. However, there was no improvement in clinical signs after treatment with mitotane in the female dog, which died 2 months after diagnosis. Histological evaluation confirmed the presence of adrenocortical carcinoma in both dogs.

In cats, secretion of progesterone by adrenocortical tumours has been reported in several case reports and case series.[20,24–26] Although they were usually associated to hyperaldosteronism, in a few cases only progesterone secretion was demonstrated.[24,25] Clinical signs including polyuria, polydipsia, alopecia and diabetes mellitus that would be expected in hyperadrenocorticism were reported in most cases. In the cats treated by adrenalectomy, the clinical signs (alopecia, polyuria, polydipsia, diabetes mellitus) resolved rapidly, and in the absence of metastases, their prognosis was generally good. No cases of progesterone-producing adrenocortical tumours have been reported in other veterinary species. Other sex hormones, but not progesterone, are produced in association with hyperadrenocorticism in ferrets.[27]

Both cases described in this case report had normal blood glucose (5.2 and 4.9 mmol/L, respectively) and had no glucosuria. Unlike most cases of cats with progesterone-secreting adrenocortical tumours, these two dogs did not have diabetes mellitus associated to the excessive production of progesterone. Although hyperaldosteronism usually causes hypertension and electrolytic changes, some cats with hyperaldosteronism and hyperprogesteronism previously described had normal blood pressure and electrolytes.[20] We did not measure aldosterone in the cases described in this report, and we cannot rule out concomitant hyperaldosteronism in these patients.

There are only few reports of progesterone-secreting adrenocortical tumours in humans, with other intermediate steroids usually being also increased in these cases.[13–17] Clinical signs usually include menstrual disorders with amenorrhea or oligomenorrhea in women. There is no report of this tumour in a human male patient. Progesterone levels and clinical signs resolved after resection of the adrenal tumour or adrenalectomy, with menstruations occurring a few weeks following surgery. In four human cases, these progesterone-secreting adrenocortical tumours were adrenocortical adenoma, with adrenocortical adenocarcinoma reported only once.[14]

This report highlights the importance of ACTH stimulation test to measure sex hormones, and progesterone concentration in these cases, for dogs with clinical signs consistent with hypercortisolism and adrenal tumours, but normal or low plasma cortisol.

AUTHOR CONTRIBUTIONS

Anais Farges and Ian K. Ramsey were the clinicians to whom these cases were referred and responsible for their diagnosis. Dave Crawford referred Case 1 having already substantially diagnosed the problem and greatly assisted in the subsequent management of this case. Carlos Adrega da Silva performed the surgery in Case 2. All authors contributed to the writing of the paper.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

ETHICS STATEMENT

No ethical approval was required for the presented cases due to its retrospective nature.

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