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CASE REPORT

Companion or pet animals

Normotensive primary hyperaldosteronism due to an adrenocortical adenoma in a dog

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Abstract

We present an 8-year-old poodle with polyuria, polydipsia and muscle weakness. Physical examination revealed no abnormalities. Laboratory alterations were hypokalemia and hypernatraemia with a low urine specific gravity. Abdominal ultrasound revealed a nodule in the right adrenal gland (diameter 0.95 cm). Systolic blood pressure was normal for several consecutive days (on average 120 mmHg). Elevated plasma aldosterone and undetectable plasma renin concentrations were diagnostic of primary hyperaldosteronism. An uncomplicated adrenalectomy was performed. Histopathological examination revealed an adrenocortical adenoma with positive expression for neuron-specific enolase but not for synaptophysin and chromogranin on immunohistochemistry. In addition, immunostaining for neuron-specific enolase was also found in cells from the normal glomerular zone of the same adrenal gland. Therefore, zona glomerulosa origin of the neoplasm was inferred. Adrenalectomy normalised laboratory abnormalities with remission of clinical signs. This report highlights the importance of not excluding the diagnosis of primary hyperaldosteronism in the absence of arterial hypertension.

BACKGROUND

Primary hyperaldosteronism (PHA) is an adrenocortical disorder characterised by autonomous adrenal hypersecretion of aldosterone. PHA is the most common adrenal disorder in cats but is rare in dogs.[1] So far, only one dog with bilateral adrenocortical hyperplasia, two dogs with an adrenocortical adenoma and three dogs with an adrenocortical carcinoma have been reported as cause of PHA.[2–5] In addition, other tumours such as deoxycorticosterone-secreting adrenocortical tumour have been reported to produce signs associated with mineralocorticoid excess.[6] Autonomous hypersecretion of aldosterone leads to increased sodium and water retention and increased (renal) potassium excretion, which may result in systemic arterial hypertension and potassium depletion, respectively. All dogs with PHA reported so far had hypokalemia associated with muscle weakness and systemic arterial hypertension. To the authors' knowledge, this is the first report of a dog with normotensive PHA.

CASE PRESENTATION

An 8-year-old, neutered, female poodle (Figure 1a) with a bodyweight of 5 kg was referred because of severe polyuria, polydipsia and episodic muscle weakness (manifested as exercise intolerance).

INVESTIGATIONS

Physical examination revealed no abnormalities. The systolic arterial blood pressure was normal on several consecutive days (on average 120 mmHg, oscillometer method, SunTech Vet 20) following the protocol and recommendations described in the ACVIM consensus statement.[7] Routine blood examination revealed elevated alkaline phosphatase activity (425 IU/L, RI: <250 IU/L) and sodium concentration (156 mmol/L, RI: 143–153 mmol/L) and a low potassium concentration (3.6 mmol/L, RI: 4.0–5.4 mmol/L). Urinary specific gravity was very low (USG: 1.004). Blood biochemistry data and protein:creatinine ratios are attached as Supporting Material. Abdominal ultrasound evaluation revealed enlargement of the caudal pole of the right adrenal gland (with a diameter of 0.95 cm, Figure 1b) without reduction in the thickness of the ipsilateral cranial pole or contralateral adrenal gland. No local invasion (phrenic vein or caudal cava) was observed. A CT scan of the thorax and abdomen was suggested, but was refused by the owner, so a thorax radiograph was performed, with no evidence of abnormalities.

The results of a low-dose dexamethasone suppression test (LDDST: basal: 55.1 nmol/L; 4 hours: 2.7 nmol/L; 8 hours: 2.7 nmol/L) in conjunction with lack of polyphagia and dermatological signs was inconsistent with diagnosis of Cushing's syndrome. Moreover, an unsuppressed plasma adrenocorticotropic hormone concentration (7.7 pmol/L, RI:

1.3–14.3 pmol/L) indicated the absence of a cortisol-secreting adrenocortical tumour.[8] Plasma concentration of ACTH (Immulite 2000 analyser) and plasma cortisol (Immulite 1000 analyser, Siemens) were measured by a chemiluminescent immunometric assay, previously validated for dogs.[9,10]

Plasma concentrations of aldosterone and renin were measured by a chemiluminescent immunometric assay (Liaison, DiaSorin). A very high plasma aldosterone concentration (PAC >2770 pmol/L), compared to a group of 10 dogs that was used as control (RI: 71.7–515.2 pmol/L), was found in this case. The plasma renin concentration was compared to the plasma renin of the same population of dogs, being undetectable (PRC <0.5 μIU/ml). A reference value for renin was not established, as only in one of the dog's renin concentrations were detectable (0.6 μIU/ml). These findings were consistent with PHA.

LEARNING POINTS/TAKE HOME MESSAGES

- Dogs with primary hyperaldosteronism may be normotensive.
- Polyuria-polydipsia is an important clinical sign in canine primary hyperaldosteronism.
- Hyperaldosteronism in dogs with adrenal neoplasia should be ruled out after excluding cortisol-secreting tumour and pheochromocytoma.
- Immunostaining with an antibody against neuronal-specific enolase is helpful in the diagnosis of an aldosteronoma.
- Adrenalectomy should be considered for treatment of primary hyperaldosteronism due to a functional adrenocortical tumour.

DIFFERENTIAL DIAGNOSIS

Based on the clinical signs, the biochemical findings (hypernatraemia and hypokalemia) and the adrenal nodular imaging, an aldosterone- or cortisol-secreting tumour was suspected. Although less likely due to the absence of hypertension or arrhythmias, pheochromocytoma was also considered. Non-secretory adrenal neoplasia (true incidentaloma) was also considered, but seemed unlikely because of the presence of polyuria and polydipsia. Metastasis to the adrenal gland was also considered.

TREATMENT

Because metastases were not detected and there was no extension into large blood vessels, adrenalectomy was considered the treatment of choice. The absence of systemic arterial hypertension and the moderate hypokalemia did not require pre-surgical medical treatment with spironolactone, amlodipine or oral potassium supplementation. Blood gas analysis was performed on the day of surgery, and the serum potassium concentration was again slightly low (3.7 mmol/L, RI: 4.0–5.4 mmol/L). Unilateral adrenalectomy was performed without complications. Macroscopic examination revealed a 9 mm nodule in the caudal pole of yellowish colour (Figure 1c). Once the adrenal gland was removed, an intravenous dose of dexamethasone (0.2 mg/kg) was immediately administered, which is part of our hospital protocol used to prevent the possibility of glucocorticoid deficiency. Eight hours after adrenalectomy, the plasma concentrations of sodium and potassium were within the reference range, so supplementation with mineralocorticoids was not necessary at that time. An oral prednisolone dose of 0.25 mg/kg was continued at home and gradually tapered over 10 days as part of the same protocol.

OUTCOME AND FOLLOW-UP

Histological sections of the adrenal gland were routinely prepared and stained with haematoxylin and eosin. The histopathological diagnosis was an adrenocortical adenoma, which was constituted by a proliferation of well-differentiated cells (Figure 2), partially enclosed by a thin and incomplete connective tissue capsule. Some areas of the zona glomerulosa not affected by neoplasia exhibited moderate atrophy. Immunohistochemical staining was performed by using the Avidin-biotin complex (ABC) method coupled to peroxidase.

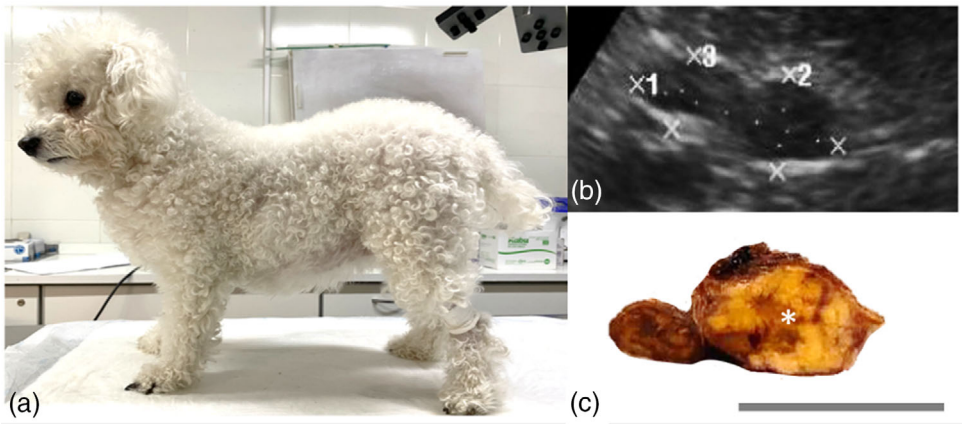

FIGURE 1 An 8-year-old, female, neutered, poodle dog presented because of polyuria-polydipsia, muscle weakness and exercise intolerance (a). Ultrasound image of the right adrenal gland with enlarged caudal pole with a diameter of 0.95 cm (b). Macroscopic appearance of the right adrenal gland after surgery in sagittal section. The neoplasm in the caudal pole (asterisk) has a yellowish colour (c)

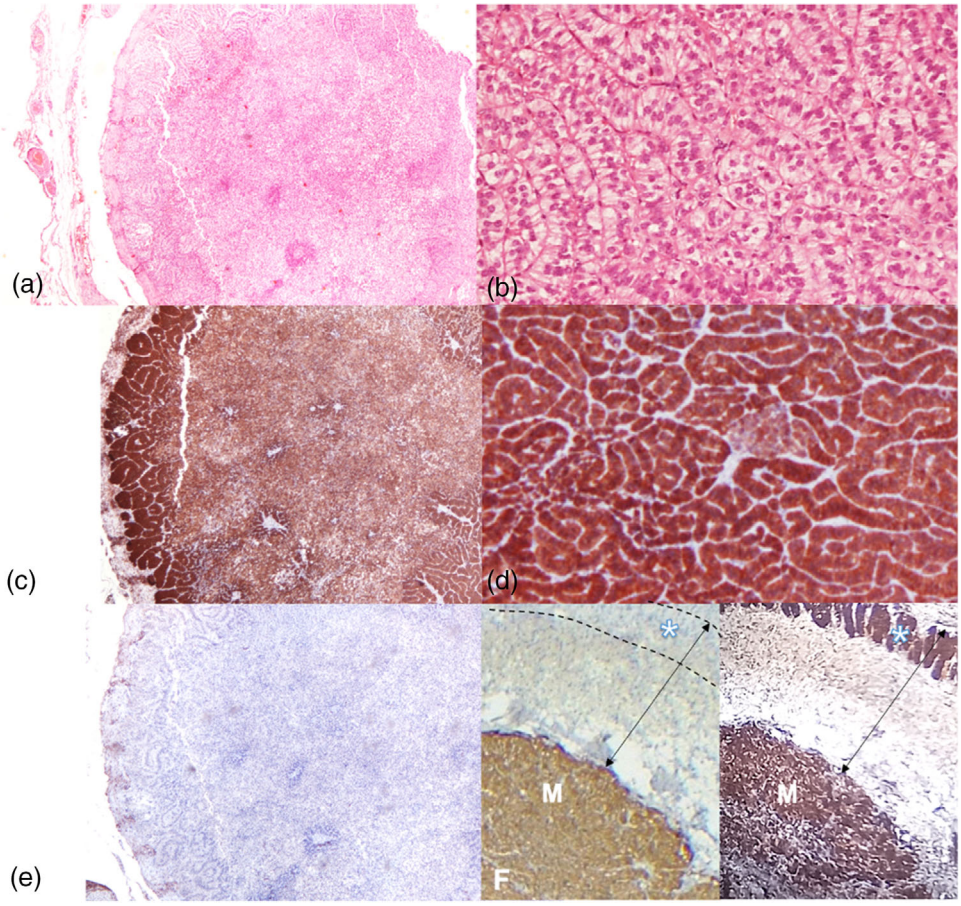

FIGURE 2 Microscopic appearance of the adrenocortical adenoma; haematoxylin–eosin (a and b). The cells of the neoplasm are large, with abundant vacuolated cytoplasm and small ovoid to slightly flattened nuclei (b). Positive immunohistochemistry (IHC) (brown) for neuron-specific enolase (c and d) and negative IHC for synaptophysin (e) in neoplastic cells. (f) A comparative image of the adrenal cortex and medulla unaffected by the adenoma is shown. On the right, neuron-specific enolase-positive IHC is present only in the atrophied zona glomerulosa (asterisk) of the adrenal cortex (arrow) and in the adrenal medulla (M), whereas on the left, IHC for synaptophysin was only positive in the adrenal medulla, but not in the adrenal cortex

Adrenal sections were incubated with primary antibodies to neuron-specific enolase (NSE, PA0435, monoclonal mouse anti-human, Clone 22C9, Leica Biosystems; 1:50), synaptophysin (SYNAP-299-L-CE, monoclonal mouse anti-human, Clone 27G12, Leica Biosystems; 1:50) and chromogranin A (CHROM-430-L-CE, monoclonal mouse anti-human, Clone 5H7, Leica Biosystems; 1:50). Immunoreactivity was revealed with diaminobenzidine and counterstained with haematoxylin. Cells constituting the neoplasm and unaffected cells from the glomerular zone of the same adrenal gland showed intense cytoplasmic immunostaining for NSE, but not for the neuroendocrine markers synaptophysin and chromogranin A (Figure 2c–e). In addition, immunostaining for NSE and synaptophysin was also found in normal adrenal medulla cells (Figure 2f). These immunohistochemical results supported the zona glomerulosa origin of the neoplasm, and pointed to an aldosteronoma, as well as ruling out the possibility of a pheochromocytoma. Two normal adrenal glands from a dog (euthanased due to trauma) were used as positive tissue controls for NSE, synaptophysin and chromogranin A.

One month after adrenalectomy, the polyuria-polydipsia and the exercise intolerance had resolved. Likewise, laboratory investigation revealed marked improvement in USG (1.023, previously 1.004) with normalisation of plasma alkaline phosphatase activity (148 IU/L, RI: <250 IU/L) and plasma concentrations of sodium (146 mmol/L, RI:143–153 mmol/L) and potassium (4.6 mmol/L, RI: 4.0–5.4 mmol/L). The PAC had decreased considerably (1163 pmol/L, RI: 71.7–515.2 pmol/L), whereas the PRC was not suppressed anymore (1.5 μUI/ml) (Table 1).

One year after adrenalectomy, telephone communication with the owner and veterinarian reported absence of the initial clinical signs, absence of arterial hypertension and normal plasma sodium and potassium concentrations (143 mmol/L, RI:143–153 mmol/L and 4.5 mmol/L, RI: 4.0–5.4 mmol/L, respectively) with a urinary specific gravity of 1.028.

DISCUSSION

In this case report, we describe a dog with an aldosterone-secreting adrenocortical adenoma, aldosteronoma, without systemic arterial hypertension. The adrenocortical neoplasm produced aldosterone autonomously and independently of the renin-angiotensin system, as illustrated by the suppressed PRC, and is therefore called PHA.[11] In contrast, secondary hyperaldosteronism, which is the most common form of hyperaldosteronism in dogs, occurs because of stimulation of the renin-angiotensin system that ultimately results in increased aldosterone secretion by the adrenal gland, for example, due to hypovolemia. In our case, the diagnosis of PHA was made based on (a) confirmation of a very high plasma aldosterone concentration in combination with an

undetectable plasma renin concentration; (b) absence of clinical and physical signs associated with Cushing's syndrome; (c) exclusion of a pheochromocytoma by immunohistochemistry (negative chromogranin and synaptophysin staining); and (d) positive immunostaining with NSE in cells of the adrenal tumour as well as of the cells of the non-affected glomerular zone of same adrenal gland, suggested the glomerular origin of the neoplasm.

Antibodies specifically directed to enzymes involved in steroidogenesis (CYP11B1: cortisol and CYP11B2: aldosterone) are currently used to demonstrate that a tumour is aldosterone producing in humans.[5,12] However, the canine adrenal cortex appears to have a single *CYP11B* gene that is expressed in both the glomerular and fascicular zones. The use of antibodies targeting AGTR2 (angiotensin II receptor 2), DAB2 (disabled-2) and Wnt4 (wingless-type MMTV integration site family, member 4) have been suggested as markers for the canine glomerular zone and could therefore be used in future cases for the diagnosis of canine aldosteronoma.[13] In contrast to humans, there is evidence that NSE stains only the zona glomerular of the normal adrenal cortex in dogs and cats, so immunostaining for NSE was used in our case.[3,14,15] Likewise, in the most complete case reported to date of an aldosterone-producing adenoma by Rijnberk et al., immunostaining for NSE was positive.[3] On the other hand, in human and veterinary medicine, NSE has been used mainly as a neuroendocrine marker, so that positive immunostaining is found in normal adrenal medulla and in tumours arising from it such as pheochromocytoma. However, negative immunostaining for synaptophysin and chromogranin A excluded a neuroendocrine origin in this case.[14] Likewise, the atrophy of the glomerular area not affected by the neoplasm suggested excessive production of aldosterone by the tumour.

The clinical signs and biochemical findings in dogs with hyperaldosteronism are comparable with those in canine hypercortisolism. Polyuria, polydipsia, hypokalemia and increased plasma activity of alkaline phosphatase are common findings in both conditions.[3] Although some dogs with hypercortisolism may present with a normal LDDST, in our dog the absence of physical features of Cushing's syndrome, no suppression of endogenous ACTH in the context of an adrenal tumour, and no reduction in size of the contralateral adrenal gland and ipsilateral pole make the diagnosis of hypercortisolism unlikely.[4,8]

A remarkable observation in our dog was a normal arterial blood pressure. In human medicine, normotensive PHA is unusual. Reasons why the arterial blood pressure may be normal despite excessive aldosterone secretion include early diagnosis of hyperaldosteronism before the development of hypertension, salt restriction, a lower level of the vasoconstrictor system or a higher level of the vasodilator system, and patients with a low range of normal blood pressure developing PHA.[16] Various genes involved in blood pressure regulation may protect some PHA patients from developing arterial hypertension.[17] Based on the very few reports of PHA in canine medicine it is difficult to know whether normotensive PHA is a common finding in dogs. However, it could also be frequent, if compared to what occurs in some cats with aldosterone-producing tumours.[18]

Medical treatment with aldosterone receptor blockers only attenuates the clinical signs but does not cure the disease. In our dog, it was not needed to start medical therapy. Adrenalectomy can be a curative option, and this was the treatment instituted. The right adrenal gland was removed completely and follow-up revealed complete resolution of clinical signs. Despite resolution of clinical signs, the PAC 1 month after therapy was 1163 pmol/L, which is higher than the reference interval from our laboratory. This may be related to the breed, as the normal values of PAC from poodle dogs has been reported to be 185.5–1246.5 pmol/L.[19] The absence of PRC suppression also argues against PHA after adrenalectomy.

In conclusion, the diagnosis of PHA in our dog was based on fitting clinical signs and routine laboratory findings, a very high PAC in combination with suppressed PRC, and positive immunohistochemical staining for neuron-specific enolase. This case report also highlights that PHA should not be excluded when the arterial blood pressure is not elevated.

TABLE 1 Functional adrenocortical evaluation pre- and post-adrenalectomy

Analyte	Pre-adrenalectomy	Post-adrenalectomy	Reference interval
Plasma cortisol 8 hours post-dex (LDDST) (nmol/L)	2.7	np	<33.1
Plasma endogenous ACTH concentration (pmol/L)	7.7	2.8	1.3–14.3
Plasma aldosterone concentration (pmol/L)	>2770	1163	71.7–515.2
Plasma renin concentration (μUI/ml)	<0.5	1.5	<0.5
Plasma sodium concentration (mmol/L)	156	146	143–153
Plasma potassium concentration (mmol/L)	3.6	4.6	4.0–5.4
Urine specific gravity	1.004	1.023	>1.025

Abbreviations: ACTH, adrenocorticotropin hormone; LDDST, low-dose dexamethasone suppression test.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

FUNDING INFORMATION

The authors received no specific funding for this work.

ETHICS STATEMENT

The work described in this manuscript involved the use of non-experimental animals. Established internationally recognised high standards ('best practice') of veterinary clinical care were used for the individual. Ethical approval from a committee was therefore not specifically required for publication in Vet Record Case Reports. Additionally, written consent was obtained from owner for their subsequent publication.

AUTHOR CONTRIBUTIONS

Santiago Teyssandier and Elber Alberto Soler Arias acquired the data and designed the case. All authors interpreted the results and wrote the case report.

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REFERENCES

1. Djajadiningrat-Laanen SC, Galac S, Kooistra H. Primary hyperaldosteronism. J Feline Med Surg. 2011;13(9):641–50.
2. Breitschwerdt EB, Meuten DJ, Greenfield CL, Anson LW, Cook CS, Fulghum RE. Idiopathic hyperaldosteronism in a dog. J Am Vet Med Assoc. 1985;187:841–5.
3. Rijnberk A, Kooistra HS, Van Vonderen IK, Mol JA, Voorhout G, van Sluijs FJ, et al. Aldosteronoma in a dog with polyuria as the leading symptom. Domest Anim Endocrinol. 2001;20:227–40.
4. Feldman EC, Nelson RW. Hyperadrenocorticism. Canine and Feline Endocrinology and Reproduction. Elsevier Health Sciences; 2003: 390–1
5. Johnson KD, Henry CJ, McCaw DL, Turnquist SE, Stoll MR, Kiupel M, et al. Primary hyperaldosteronism in a dog with concurrent lymphoma. J Vet Med A Physiol Pathol Clin Med. 2006;53:467–70.
6. Reine NJ, Hohenhaus AE, Peterson ME, Patnaik AK. Deoxycorticosterone-secreting adrenocortical carcinoma in a dog. J Vet Intern Med. 1999;13:386–90.
7. Acierno MJ, Brown S, Coleman AE, Jepson RE, Papich M, Stepien RL, et al. ACVIM consensus statement: guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. J Vet Intern Med. 2018;32:1803–22.
8. Rodríguez Piñeiro MI, Benchekroun G, de Fornel-Thibaud P, Maurey-Guenec C, Garnier F, Rosenberg D. Accuracy of an adrenocorticotropic hormone (ACTH) immunoluminometric assay for differentiating ACTH-dependent from ACTH-independent hyperadrenocorticism in dogs. J Vet Intern Med. 2009;23:850–5.
9. Scott-Moncrieff JC, Koshko MA, Brown JA, Hill K, Refsal KR. Validation of a chemiluminescent enzyme immunometric assay for plasma adrenocorticotropic hormone in the dog. Vet Clin Pathol. 2003;32:180–7.
10. Singh AK, Jiang Y, White T, Spassova D. Validation of nonradioactive chemiluminescent immunoassay methods for the analysis of thyroxine and cortisol in blood samples obtained from dogs, cats, and horses. J Vet Diagn Invest. 1997;9:261–8.
11. Kooistra HS. Primary hyperaldosteronism in cats: an underdiagnosed disorder. Vet Clin North Am Small Anim Pract. 2020;50:1053–63.
12. Gomez-Sanchez CE, Gomez-Sanchez EP. Immunohistochemistry of the adrenal in primary aldosteronism. Curr Opin Endocrinol Diabetes Obes. 2016;23:242–8.
13. Sanders K, Mol JA, Kooistra HS, Slob A, Galac S. New insights in the functional zonation of the canine adrenal cortex. J Vet Intern Med. 2016;30(3):741–50.
14. Galac S, Korpershoek E. Pheochromocytomas and paragangliomas in humans and dogs. Vet Comp Oncol. 2017;15:1158–70.
15. Javadi S, Djajadiningrat-Laanen SC, Kooistra HS, van Dongen AM, Voorhout G, van Sluijs FJ, et al. Primary hyperaldosteronism, a mediator of progressive renal disease in cats. Domest Anim Endocrinol. 2005;28:85–104.
16. Moradi S, Shafiepour M, Amirbaigloo A. A woman with normotensive primary hyperaldosteronism. Acta Med Iran. 2016;54:156–8.
17. Médeau V, Moreau F, Trinquart L, Clemessy M, Wémeau JL, Vantyghem MC, et al. Clinical and biochemical characteristics of normotensive patients with primary aldosteronism: a comparison with hypertensive cases. Clin Endocrinol. 2008;69:20–8.
18. Ash RA, Harvey AM, Tasker S. Primary hyperaldosteronism in the cat: a series of 13 cases. J Feline Med Surg. 2005;7:173–82.
19. Pedersen HD, Olsen LH, Arnorsdottir H. Breed differences in the plasma renin activity and plasma aldosterone concentration of dogs. J Vet Med A. 1995;42(1–10):435–41.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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