NOTE *Internal Medicine*

Aldosterone-, Corticosterone- and Cortisol-Secreting Adrenocortical Carcinoma in a Dog: Case Report

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ABSTRACT. A 12-year-old, intact female beagle exhibited symptoms of polyuria-polydipsia and hyperorexia for two months. Blood tests showed elevated asparate aminotransferase, alanine aminotransferase, alkaline phosphatase and creatine kinase levels, as well as marked hypokalemia. The results of adrenocorticotropic hormone stimulation test showed elevated cortisol, aldosterone and corticosterone concentrations. Abdominal ultrasonography confirmed a mass in the left adrenal gland. Masses were also seen in the liver and caudal vena cava. Diagnosis was a tumor of the adrenal cortex with metastases. Trilostane administration was initiated. The dog initially showed improved demeanor as a result of regulating hormone secretion. However, after 88 days, the dog weakened rapidly, before dying on the 117th day. Pathological findings confirmed a diagnosis of adrenocortical carcinoma.

KEY WORDS: adrenocortical carcinoma, aldosterone, canine.

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About 15% of hyperadrenocorticism (HAC) cases in dogs are functional adrenocortical adenoma and carcinoma [4]. In most cases, the hormone secreted by tumors in the adrenal cortex is cortisol, which is a glucocorticoid. However, functional adrenal cortex tumors secreting aldosterone and corticosterone are very rare [1, 2]. This report describes a dog diagnosed as having aldosterone-, corticosterone- and cortisol-secreting adrenocortical carcinoma, which was treated with trilostane.

A 12-year-old intact female beagle weighing 12.9 kg exhibited symptoms of polyuria-polydipsia, hyperorexia and decline in vigor for two months. On physical examination, vital signs were normal, but a poor coat, thin skin and potbelly were seen. In addition, cardiac murmur in the shrinkage period (levain 3/6) was observed.

Complete blood count and serum biochemical analyses were performed. Hematologic and biochemical abnormalities included slightly high WBC count, high asparate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and creatine kinase (CK) activities, and hypokalemia (Table 1).

Abdominal ultrasonography confirmed the presence of an irregular mass in the marginal left adrenal gland. Masses were also seen in the liver and the caudal vena cava, and this latter mass caused circulatory disruption. The right adrenal gland was normal.

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The results of adrenocorticotropic hormone stimulation test (ACTH-ST) were as follows (Table 2). Serum cortisol was measured with a commercially available competitive enzyme immunoassay (TOSOH AIA-360 system analyzer, Tosho Co., Tokyo, Japan). Measurement of plasma aldosterone and serum corticosterone was performed by the Kishimoto Clinical Laboratory group. Basal cortisol concentration was 119 nM/*l*, but rose to 855 nM/*l* at 60 min after intramuscular injection of 0.25 mg of cosyntropin. Basal plasma aldosterone concentration (PAC) was 3,601 pM/*l*, but rose to 15,235 pM/*l* at 30 min and to 20,755 pM/*l* at 60 min after stimulation. Basal serum corticosterone concentration was 52 nM/*l*, but rose to 105 nM/*l* at 30 min and to 1,332 nM/*l* at 60 min after stimulation. Cortisol, aldosterone and corticosterone concentrations in this case showed marked increases within 30 and 60 min of ACTH-ST when compared with control dogs (Table 2).

Diagnosis was hypercorticoidism, hyperaldosteronism and hypercorticosteronism originating in the left adrenal tumor. In this case, metastasis into the liver was already present. After a discussion with the owner, medication rather than surgery was selected, and trilostane administration was initiated (60 mg/head, orally at 7 a.m., once daily). The dose of trilostane administration was based on previous reports [3, 4, 7, 9].

On the 20th day, the dog's appetite and polyuria-polydipsia had improved, and typical life activities were possible. AST and CK activity, and electrolytes returned to normal values, and ALP activity showed a marked decrease. The results for ACTH-ST stimulation on the 20th day are shown in Table 2. Cortisol concentration was normal before (34 nM/*l*) and after (230 nM/*l*) ACTH-ST, but aldosterone and corticosterone concentrations were abnormal after ACTH-ST (8,864 pM/*l* and 682 nM/*l*, respectively). On the 55th

Table 1. Hematology and biochemistry results at various days after diagnosis and during treatment

Blood parameter	Value					Range
Days from start of treatment	1	20	55	88	106	
White blood cells ($\times 10^9/l$)	**13.9**[a)]	9.3	8.1	**18.9**	**32.9**	4.7 – 12.0
Neutrophils ($\times 10^9/l$)	**12.4**	8.3	7.6	**16.6**	**28.6**	1.6 – 11.7
Lymphocytes ($\times 10^9/l$)	**1.3**	**0.5**	**0.2**	**1.7**	3.3	1.9 – 5.5
Monocytes ($\times 10^9/l$)	0.2	0.2	0.2	0.6	1.0	0.2 – 1.7
Eosinophils ($\times 10^9/l$)	0	0.3	0.1	0	0	0 – 0.8
Red blood cells ($\times 10^{12}/l$)	**8.9**	**9.2**	**8.4**	7.4	**4.1**	5.8 – 7.7
Hemoglobin (g/*l*)	165	168	153	**129**	**75**	145 – 196
Packed cell volume (%)	**55**	**55**	50	44	**24**	37 – 52
Sodium (mM/*l*)	154	147	149	148	**143**	145 – 155
Potassium (mM/*l*)	**2.5**	3.6	3.8	**3.3**	3.6	3.5 – 5.0
Chloride (mM/*l*)	**128**	119	115	115	116	108 – 120
Alkaline phosphatase (IU/*l*)	**4,016**	**1,945**	**1,452**	**7,660**	**10,740**	10 – 143
Alanine aminotransferase (IU/*l*)	**272**	**131**	**87**	**426**	**462**	10 – 48
Aspartate aminotransferase (IU/*l*)	**102**	31	25	**67**	**105**	10 – 56
Creatine kinase (IU/*l*)	**593**	45	59	64	139	10 – 150
Calcium (mM/*l*)	2.7	2.7	2.7	2.5	2.4	2.0 – 3.0
Phosphate (mM/*l*)	**0.5**	1.0	1.0	1.0	1.6	0.8 – 2.0
Glucose (mM/*l*)	6.5	5.9	5.8	**6.7**	6.1	3.6 – 6.6
Total protein (g/*l*)	68	70	63	55	**48**	54 – 73
Albumin (g/*l*)	37	39	36	32	28	27 – 40
Creatinine (μM/*l*)	**62**	**62**	71	**62**	**44**	68 – 104
Urea (mM/*l*)	2.9	2.5	3.2	2.1	5.7	1.8 – 9.0

a) Abnormal results are given in bold.

Table 2. ACTH stimulation test results

Timing of test Day	Serum cortisol concentration (nM/*l*)			Plasma aldosterone concentration (pM/*l*)			Serum coriticosterone concentration (nM/*l*)		
	ACTH injection			ACTH injection			ACTH injection		
	Basal	After 30 min	After 60 min	Basal	After 30 min	After 60 min	Basal	After 30 min	After 60 min
1	**119.3**[a)]	**548**	**855**	**3,601**	**15,235**	**20,755**	**52**	**105**	**1,332**
20	34	131	230	**748**	**6,648**	**8,864**	11	**491**	**682**
55	9	31	40	302	723	**2,208**	NT[c)]	NT	NT
Reference range[b)]	8.0–50	254–378	400–524	211–355	729–1,391	418–1,000	4.0–23.9	38.9–73.1	42.3–78.3

Dosage of trilostane was 60 mg/head once daily at all time points.
a) Abnormal results are given in bold.
b) Values based on ACTH stimulation test results in 6 clinically normal beagles.
c) Not tested.

day, the owner's assessment of the dog's appetite, thirst and general stamina was also taken into consideration. Cortisol and aldosterone concentrations were markedly reduced after ACTH-ST when compared with the first day (Table 2). However, on the 88th day, the dog again began to show polyuria-polydipsia, and pendulous abdomen was larger than on the 55th day. Hematologic and biochemical abnormalities included high WBC count, AST, ALT and ALP activities, and anemia (Table 1). Abdominal ultrasonography revealed that the liver and adrenal gland masses had increased in size. Furthermore, on the 106th day, WBC count, AST, ALT and ALP activities had increased further, and anemia had worsened (Table 1). Subsequently, the dog weakened rapidly, and died on the 117th day.

Pathological findings confirmed that the neoplasm involved the left kidney, and was located in the left renal vein-caudal vena cava bifurcation. The neoplasm metastasized to the lobus hepatis, the lobus caudalis of both lungs, and the valva tricuspidalis. The adrenal cortical carcinoma comprised large and polyhedral neoplastic cells that resembled steroid hormone-producing cells. The neoplastic cells were arranged in nests separated by a fine fibrovascular stroma. They had large and round nuclei with eosinophilic vacuolated cytoplasm (Fig. 1A). Metastatic adrenal cortical carcinoma was present within the liver and lung, and hepatic parenchyma being compressed by neoplastic cells was seen on the right side (Figs. 1B, C). The tissue consisted of uniform sheets of secretory cells with delicate fibrovascular stroma and widely scattered, dilated vascular sinusoids.

The clinical signs of this case included polyuria-polydipsia, alopecia and potbelly, while severe hypokalemia was also seen. Moreover, weakness was one of the initial signs

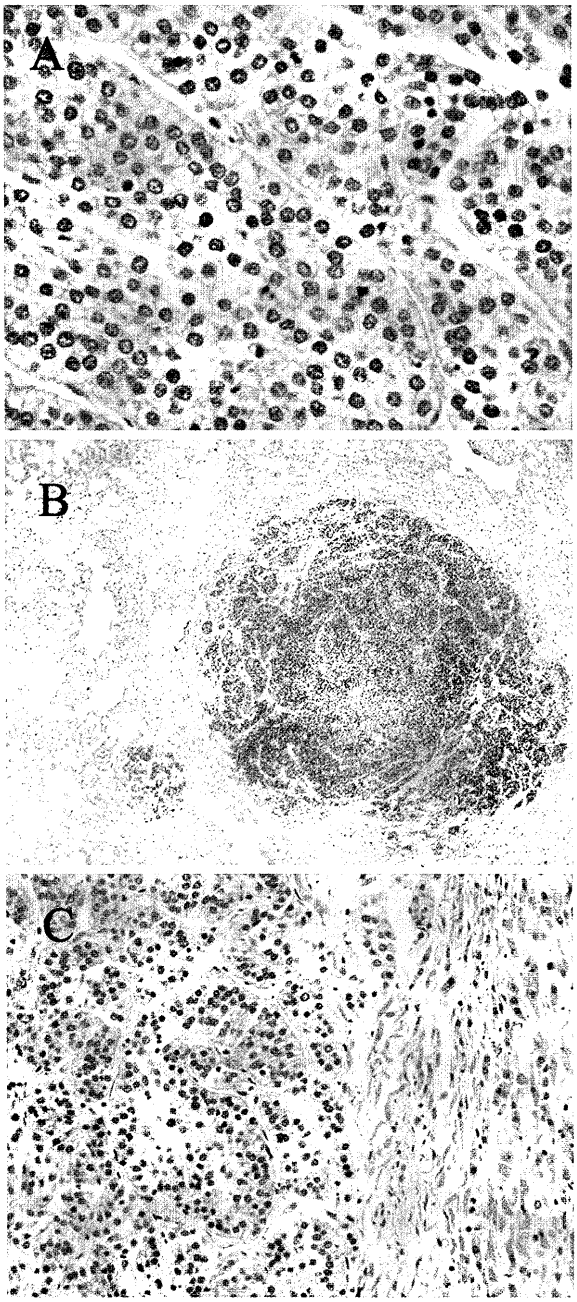

Fig. 1. (A) Adrenal cortical carcinoma is composed of large and polyhedral neoplastic cells that resemble steroid hormone-producing cells. Neoplastic cells are arranged in nests separated by a fine fibrovascular stroma. They have large and round nuclei with eosinophilic vacuolated cytoplasm. HE stain. × 400. (B) Metastatic adrenal cortical carcinoma is present in the lung. HE stain. × 40. (C) Metastatic adrenal cortical carcinoma is present in the liver. Hepatic parenchyma compressed by neoplastic cells can be seen on the right. HE stain. × 100.

in this case. Abdominal ultrasonography confirmed the presence of a marginal irregular mass in the left adrenal gland. It was temporarily diagnosed as adrenal-dependent hyperadrenocorticism (ADH) induced by adrenal tumor (AT). Neither weakness nor hypokalemia have been reported with excessive cortisol secretion, which is a feature of HAC [4]. After ACTH-ST was performed, it was confirmed that secretion of cortisol, aldosterone and corticosterone were elevated. It has been reported that aldosterone tends to be decreased, while cortisol is increased, in pituitary or adrenal tumor HAC [1, 2, 8]. Moreover, increased corticosterone is not reportedly present with HAC [1, 2]. Adrenocortical carcinoma secreting cortisol, aldosterone and corticosterone has not been reported in dogs, and thus the present case was very unusual.

Fluctuations in cortisol, aldosterone and corticosterone concentrations after ACTH-ST were compared between the present case and six healthy dogs. In the healthy dogs, the concentrations of these hormones were the same as in other reports [1, 2, 5, 6, 8]. Cortisol concentrations peaked at 60 min after ACTH-ST, and this was in agreement with previous reports. However, it was confirmed that aldosterone concentrations peaked at 30 min after ACTH-ST, and decreased afterwards. This indicates that 30 min is more suitable than 60 min to measure aldosterone concentrations after ACTH-ST. Peak corticosterone concentrations were seen at 60 min after ACTH-ST.

Pathologic diagnosis of adrenocortical carcinoma in humans is based on Weiss's criteria [10], and a tumor must meet three of the nine criteria. The present case met more than three of these criteria, and was thus diagnosed as adrenocortical carcinoma.

Trilostane obstructs hormone synthesis by inhibiting 3-β-hydroxysteroiddehydrogenase, which is common to the synthesis of glucocorticoids, mineralocorticoids and sex hormones in the adrenal cortex. It also acts in a reversible manner. In this case, aldosterone reduction was required, and trilostane was thus used.

Potassium concentrations showed a normal range at the start of trilostane administration. Subsequent ACTH-ST confirmed sufficient inhibition of cortisol secretion on the 20th and 55th days. Although aldosterone concentration before ACTH-ST was within the normal range on these days, excess secretion was seen at 30 and 60 min after stimulation. With regard to corticosterone, as with aldosterone, it was normal before ACTH-ST, but showed excessive secretion after ACTH-ST. This suggests that trilostane inhibits cortisol synthesis more strongly than aldosterone and corticosterone synthesis; it was previously thought that there were differences in suppression of the various adrenocortical hormones. This also appears to support a previous report suggesting that trilostane is predominantly distributed in the zona fasciculate, rather than in the zona glomerulosa, after administration [11].

Trilostane is prescribed as a treatment for PDH, and is reported to suppress cortisol and aldosterone secretion [7, 9]. One report has discussed its prescription for functional

adrenocortical neoplasm [3]. In this case, a temporary lull state was observed, as the present adrenocortical carcinoma showed cortisol, aldosterone and corticosterone secretion. The present case suggests the utility of trilostane in ADH induced by AT. However, further study on the use of trilostane is necessary.

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