Corticosterone- and aldosterone-secreting adrenocortical tumor in a dog

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- Adrenocortical tumors in dogs may produce a combination of glucocorticoids and mineralocorticoids.
- Adrenocortical tumors in dogs may produce glucocorticoids other than cortisol.

An 11-year-old 45-kg (99-lb) spayed female Doberman Pinscher was referred to the Small Animal Clinic of Auburn University with a 3-month history of weakness, occasional proprioceptive deficits in the hind limbs, polyuria-polydipsia, an enlarged abdomen, and bilateral truncal alopecia. On the basis of physical appearance and clinical signs, high serum **alkaline phosphatase (ALP)** activity, and urine specific gravity of 1.001, the referring veterinarian made a tentative diagnosis of **hyperadrenocorticism (HAC)**, but no further diagnostic tests or treatment were performed.

On physical examination, rectal temperature was 38.9°C (102°F), heart rate was 130 beats/min, and respiratory rate was 30 breaths/min. The abdomen was pendulous. The skin was thin with diffuse alopecia and no evidence of erythema or pyoderma. The dog was unable to rise without assistance, and marked cervical ventroflexion was noted. Neurologic examination revealed muscle weakness and ataxia with decreased reflexes in all 4 limbs. Cranial nerve assessment revealed normal findings.

A CBC, serum biochemical analyses, urinalysis, and bacteriologic culture of urine were performed. Hematologic abnormalities included high WBC count (29,700 cells/µL; reference range, 6,000 to 17,000 cells/µL) with neutrophilia (28,500 cells/µL; reference range, 3,000 to 11,500 cells/µL), lymphopenia (0 cells/µL; reference range, 1,000 to 4,800 cells/µL), and eosinopenia (0 cells/µL; reference range, 200 to 1,400 cells/µL); high serum alanine aminotransferase activity (73 U/L; reference range, 17 to 66 U/L); high serum ALP activity (690 U/L; reference range, 19 to 50 U/L); low serum BUN concentration (7 mg/dL; reference range, 10 to 25 mg/dL); hypernatremia (181 mmol/L; reference range, 142 to 150 mmol/L); hypokalemia (2.7 mmol/L; reference range, 3.9 to 5.3 mmol/L); and hyperchloremia (150 mmol/L; reference range, 110 to 121 mmol/L). Urinary abnormalities included hyposthenuria (urine specific gravity, 1.005). Results of bacteriologic culture of urine were negative.

For the dermatologic changes, differential diagnoses included HAC, hypothyroidism, growth-hormone–responsive dermatosis, and estrogen-responsive dermatosis. Because of the thin skin, hyposthenuria, and high serum ALP activity, HAC was the primary differential diagnosis. Because of hyposthenuria, normal hydration status, severe hypokalemia, and generalized weakness, hyperaldosteronism was considered. Because an adrenal gland tumor secreting cortisol and aldosterone could cause the clinical signs, thoracic and abdominal radiography, abdominal ultrasonography, and an ACTH stimulation test (250 µg cosyntropin,[a] IV; blood samples taken before and 1 hour after injection) with measurement of serum cortisol and aldosterone concentrations were performed. A plasma sample was also submitted for measurement of **endogenous ACTH (eACTH)** concentration. Blood pressure should have been measured but was not obtained because of an oversight.

On thoracic radiographs, no pulmonary metastases were seen but diffuse osteoporosis was evident. On abdominal radiographs, the right kidney was displaced ventrally and caudally by a mass effect in the retroperitoneal area near the adrenal gland. On ultrasonographic examination, an enlarged right adrenal gland was seen with possible invasion of the caudal vena cava. The liver was diffusely hyperechoic. An ultrasonographically guided hepatic aspiration was performed, and cytologic diagnosis was corticosteroid hepatopathy.

Fluid therapy was instituted (lactated Ringer's solution, 188 mL/h, IV) with 30 mEq of KCl/L. On day 2, serum sodium concentration was 159 mmol/L and serum potassium concentration was 2.7 mmol/L. Administration of potassium gluconate (15 mEq, PO, q 12 h) was initiated. On day 4, serum sodium and potassium concentrations were 155 and 3.4 mmol/L, respectively.

On day 4, results of the ACTH stimulation test were obtained and revealed basal serum cortisol concentration within reference range and a subnormal response to ACTH stimulation **(Table 1)**. Serum cortisol concentration was measured with a previously validated[1] commercially available radioimmunoassay[b] with cross-reactivity for corticosterone of 0.94%, as reported by the manufacturer. Differential diagnoses included exogenous glucocorticoid administration and an adrenal gland tumor. There was no history of exogenous glucocorticoid administration by any route.

During hospitalization, the clinical signs of weakness and cervical ventroflexion resolved as the serum

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Table 1—Serum cortisol, corticosterone, and aldosterone concentrations before and after administration of ACTH in a dog with a corticosterone- and aldosterone-secreting adrenocortical tumor. Mitotane administration was begun on day 29 after initial evaluation (day 0).

	Serum cortisol concentration (nmol/L)		Serum corticosterone concentration (nmol/L)		Serum aldosterone concentration (pmol/L)	
Day	Before ACTH	After ACTH	Before ACTH	After ACTH	Before ACTH	After ACTH
4	59	122	NA	NA	1,645	> 3,329
23	45	97	335	1,565	NA	NA
43	ND	ND	ND	ND	42	1
52	ND	ND	ND	ND	95	171
64	ND	ND	ND	ND	251	197
78	18	11	ND	ND	ND	295
Reference range	10–160	220–560	ND*	28–107*	14–957	197–2,103
Range in dogs with HAC†	27–274	747–2,525	3–43	103–830	ND	ND

*Values based on ACTH stimulation test results in 6 clinically normal Greyhounds. †Values obtained from 10 dogs with clinical signs of HAC and high serum cortisol concentration after administration of ACTH, consistent with HAC.

NA = Not applicable. ND = Not detectable. HAC = Hyperadrenocorticism.

potassium concentration increased. Thus, diagnostic testing for cervical disease was not pursued. The dog was discharged with instructions to the owners to continue potassium gluconate administration (15 mEq, PO, q 12 h) pending results of plasma eACTH and serum aldosterone measurements. While at home, serum sodium and potassium concentrations were measured daily. Although never within the reference range, serum potassium concentration was consistently > 3.0 mmol/L. Water consumption was determined to be excessive (267 mL/kg/d).

The results of the endocrine testing were obtained. Plasma eACTH was measured with a validated[2] commercially available immunoradiometric assay.[c] Plasma eACTH concentration was reported as < 6 pg/mL (reference range, 10 to 80 pg/mL), which was suggestive of a glucocorticoid-secreting adrenal gland tumor. Because of a miscommunication, a high-dose dexamethasone suppression test was performed. The baseline cortisol concentration was within reference range (56 nmol/L; reference range, 10 to 160 nmol/L), but there was no suppression (4 hours after dexamethasone administration, 53 nmol/L; 8 hours, 48 nmol/L [reference range, < 30 nmol/L at both times]).

The serum aldosterone concentration[d] was high (Table 1). Aldosterone was measured with a commercially available radioimmunoassay kit.[e] The radioimmunoassay was performed with reagent volumes and incubation conditions described in the manufacturer's protocol. Specificity data provided by the manufacturer indicated extremely low (< 0.03%) cross-reactivity with 23 selected naturally occurring or synthetic steroidal hormones, including cortisol, corticosterone, progesterone, dexamethasone, fludrocortisone, and prednisolone. The sensitivity of detection of the assay, defined as the concentration of aldosterone corresponding to the amount of bound radioactive tracer 2 SDs less than that of the zero standard, was 39 pmol/L (mean of 10 assays). When aldosterone was added at amounts of 280, 560, and 840 pmol/L to aliquots of a canine serum pool (86 pmol/L), 101%, 86%, and 85% of added aldosterone was measured in the assay, respectively. Canine serum pools of 582 and 1,020 pmol/L were diluted at rates of 50% and 12.5% in the zero standard to assess dilutional parallelism and were 108% and 116%, respectively. Assay repeatability was assessed with 3 pools of canine serum with mean concentrations of 86, 582, and 1,020 pmol/L. The respective intra-assay coefficients of variation for 10 duplicates of these pools were 19.6%, 5.3%, and 4.7%, respectively. In 10 assay runs, the interassay coefficients of variation for these pools were 17%, 5%, and 7.5%, respectively.

The dog returned on day 22 for further assessment. The dog was anesthetized, and an abdominal computed tomography scan was performed. The dog was premedicated with oxymorphone (0.2 mg/kg [0.09 mg/lb], IV), diazepam (0.22 mg/kg [0.1 mg/lb], IV), and atropine (0.022 mg/kg [0.01 mg/lb], IV). Anesthesia was induced with thiopental (15 mg/kg [6.8 mg/lb], IV) and maintained with isoflurane gas. On a computed tomography scan, a mass was seen in the right craniodorsal portion of the abdomen and was believed to originate from the right adrenal gland. Small areas of mineralization were evident in the mass, and invasion into the caudal vena cava was detected. Ultrasonographically guided biopsies of the mass were performed. Microscopic examination of the biopsy specimens revealed adrenocortical carcinoma. The tissue consisted of uniform sheets of secretory cells with delicate fibrovascular stroma and widely scattered, dilated vascular sinusoids. Individual tumor cells were polygonal with indistinct cell borders and abundant, eosinophilic, finely vacuolated cytoplasm and a centrally located, round nucleus with marginated chromatin and, often, a prominent, basophilic nucleolus. Mitotic figures were fewer than 1 in every five 400X fields. Neoplastic cells had uniform, strong, diffuse cytoplasmic binding by antibodies directed against vimentin and neuron-specific enolase and no binding by an antibody directed against cytokeratin. Results of the immunohistochemical staining supported a diagnosis of adrenal cortical carcinoma and were suggestive of neuroendocrine differentiation by the neoplastic adrenal cortical cells.

Because of lack of a history of exogenous glucocorticoid administration, the clinical appearance of the dog, high serum ALP activity, osteoporosis, low plasma eACTH concentration, and the subnormal cortisol response to ACTH stimulation, excess adrenal gland secretion of glucocorticoids from the adrenocortical

carcinoma seemed likely. We hypothesized that the glucocorticoid secreted in excess was corticosterone because it is a precursor of aldosterone.[3] Another ACTH stimulation test was performed on day 23. Serum cortisol concentrations before and after ACTH administration were slightly lower than previously (Table 1). Serum corticosterone concentration, however, was greatly increased, compared with 6 clinically normal dogs and 10 dogs with clinical signs of HAC and high serum cortisol concentrations after administration of ACTH.

Corticosterone was measured by use of a commercially available radioimmunoassay[f] according to manufacturer's instructions. The manufacturer's reported cross-reactivity for cortisol, aldosterone, 11-deoxycorticosterone, progesterone, and 17α-hydroxyprogesterone is < 1%. Dilution of the standards with canine serum yielded a mean of 78% recovery at all points. The clinically normal dogs were all young adult Greyhounds, but the 10 dogs believed to have HAC were of at least 5 breeds (Dachshund, Poodle, Miniature Doberman Pinscher, Miniature Schnauzer, mixed breed, and 1 unknown) and ranged in age from 6 to 13 years.

A diagnosis of a corticosterone- and aldosterone-secreting tumor was made. Mitotane administration was initiated (37.5 mg/kg [17.1 mg/lb], PO, q 6 h). A high dose was chosen because of the relative resistance of adrenal gland tumors[4] and the zona glomerulosa[5] to mitotane administration. Prednisone (0.5 mg/kg [0.23 mg/lb], q 24 h) was also dispensed. Because cortisol deficiency is the goal of treatment when treating an adrenal gland tumor, it is recommended to begin concurrent glucocorticoid administration.[6] On day 14 of treatment (43 days after initial evaluation), the dog was reevaluated. Daily water intake had decreased to within reference range (67 mL/kg/d). Serum sodium concentration was slightly high (154 mmol/L), but serum potassium concentration was within reference range (4.1 mmol/L). Abdominal ultrasonography was performed to assess the adrenal gland mass, and the mass had decreased in size overall and within the vena cava. An ACTH stimulation test was performed with measurement of serum cortisol, corticosterone, and aldosterone concentrations (Table 1). To further reduce the size of the mass, mitotane administration was continued as before.

The dog returned 9 days later for reevaluation (52 days after initial evaluation). Occasional vomiting was reported. Abdominal ultrasonography revealed further decrease in the size of the adrenal gland mass. An ACTH stimulation test was performed (Table 1). Mitotane and prednisone administration was continued as previously. Potassium supplementation was discontinued because serum potassium concentration was consistently within reference range and aldosterone secretion was less than reference range.

Twelve days later (64 days after initial evaluation), the dog was reevaluated. Serum sodium and potassium concentrations were within reference ranges. Abdominal ultrasonography revealed a slight decrease in the size of the adrenal gland mass. An ACTH stimulation test was performed (Table 1). Because of the relatively small change in the size of the adrenal gland mass and continued control of aldosterone and corticosterone secretion, mitotane administration was changed to a maintenance protocol (50 mg/kg [22.7 mg/lb], PO, 3 times weekly).

On day 78 after initial evaluation, the dog was reevaluated. The owners reported that the dog had done well until diffuse dermal erythema and nodules developed acutely. Serum sodium concentration was slightly greater than the reference range (151 mmol/L), and serum potassium concentration was within the reference range. An ACTH stimulation test was performed (Table 1). Although the baseline aldosterone serum concentration was undetectable, the sample obtained after ACTH administration revealed a greater response than was obtained during the previous 3 evaluations. In addition, serum cortisol concentration had been less than the reference range but was now measurable.

A dermatology consultation was obtained. Skin changes were described as papular dermatosis with coalescing macular erythema. Differential diagnoses included an adverse drug reaction, immune-mediated disease, vasculitis, folliculitis, furunculosis, and calcinosis cutis. A skin biopsy was performed and revealed multifocal dermal mineralization of collagen and elastin fibers. There was prominent pilosebaceous atrophy along with epidermal and follicular hyperkeratosis. Some sections contained large dermal infiltrates of neutrophils suggestive of pyoderma. Special stains for calcium revealed extensive dermal calcification. The final diagnosis was calcinosis cutis and pilosebaceous atrophy of skin secondary to hyperadrenocorticism.

Because of the continued control of adrenal gland hormone secretion, mitotane administration was continued as before. Prednisone administration was continued as well because of the ongoing adrenal glucocorticoid insufficiency. To treat the dog for pyoderma, ciprofloxacin was prescribed (10 mg/kg [4.54 mg/lb], PO, q 12 h for 14 days).

The dog was returned 129 days after initial evaluation for evaluation of acute tetraparesis. The dog was unable to rise without assistance and had signs of cervical pain. Serum sodium concentration was high (157 mmol/L), but serum potassium concentration was within the reference range. Neurologic examination revealed moderate paresis of the hind limbs and mild paresis of the forelimbs. Conscious proprioceptive deficits were evident in all 4 limbs and worse in the hind limbs, and crossed extensor responses were evident in the hind limbs. The lesion was believed to be most likely in the cervical portion of the spinal cord. Cervical vertebral stenosis, intervertebral disk disease, fibrocartilaginous embolus, hemorrhage, and neoplasia were differential diagnoses. Further diagnostic tests were discussed with the owners but were declined. The dog was euthanatized, and a necropsy was not permitted.

Hyperadrenocorticism refers to excess adrenal gland secretion of cortisol, either because of an adrenal gland tumor or an ACTH-secreting pituitary tumor. Secretion of other hormones from adrenocortical tumors, including sex hormones[7-9] and mineralocorticoids,[10,11] has been documented. To our knowledge, this is the first report of a dog with a corticosterone-secreting adrenal gland tumor or a tumor secreting both glucocorticoids and mineralocorticoids. The dog

had clinical and clinicopathologic features of glucocorticoid and mineralocorticoid excess.

Histologic evaluation confirmed the tumor to be of adrenocortical origin. Adrenal cortical cells are of mesodermal origin, as indicated by positive vimentin staining. Neuron-specific enolase has been used to identify endocrine cells in humans and dogs, is found in neuroendocrine cells such as adrenal medullary cells, and is expressed in some human adrenocortical adenomas and carcinomas.[12,13] An adrenal gland cortical tumor in a dog with multiple endocrine neoplasia strongly bound antibody directed against neuron-specific enolase.[14]

Hyperaldosteronism was suspected in this dog because of profound weakness, hypernatremia, and hypokalemia. Although glucocorticoid excess may cause mineralocorticoid effects,[10] hypernatremia and hypokalemia are not typically associated with HAC.[15] Hyperaldosteronism has been reported in 5 dogs.[10,16,17] Four dogs had an aldosteronoma,[10,17] and 1 had primary hyperaldosteronism.[16] Clinical signs included polyuria,[10,16] nocturia,[16] and episodic weakness.[17] The dog reported here had severe weakness and polyuria. Whether the polyuria was attributable to excess secretion of aldosterone, corticosterone, or both is unclear. Clinicopathologic abnormalities detected at initial evaluation in the dog of this report included marked hypernatremia and hypokalemia. Hypokalemia has been reported in all cases of hyperaldosteronism in dogs,[10,16,17] but hypernatremia is less consistent and has been detected in 1 other dog.[16] In humans with primary hyperaldosteronism, hypokalemia is usually evident. Serum sodium concentration is often only slightly high because with chronic hyperaldosteronemia, the cerebral osmoregulatory center has an altered set point and responds to sodium differently than in a clinically normal animal.[18]

The serum aldosterone concentrations in the dog reported here were initially markedly high. Serum aldosterone concentrations should not be high in response to HAC alone. Typically, basal serum aldosterone concentration in dogs with HAC is lower than that in clinically normal dogs and ACTH-stimulated concentrations are the same as in clinically normal dogs.[19] Diagnosis of hyperaldosteronism ideally should be made on the basis of high serum aldosterone concentrations in the presence of hypokalemia and serum renin concentration within or less than the reference range. Unfortunately, no commercial assay for measurement of canine serum renin concentrations is available. Therefore, diagnosis of primary hyperaldosteronism requires that all secondary causes of hyperaldosteronism, which include cardiovascular failure, renal failure, and severe generalized hepatocellular dysfunction, be ruled out. In the dog reported here, renal failure was ruled out by serum BUN concentration less than reference range and serum creatinine concentration within reference range. Results of cytologic examination of a liver aspirate did not support a diagnosis of severe generalized liver disease, and biochemical variables of liver function, such as serum glucose and albumin concentration, were within reference ranges. Cardiovascular failure was ruled out on the basis of results of physical examination and thoracic radiography.

A dog with a deoxycorticosterone-secreting adrenocortical carcinoma has been reported.[11] The dog had clinical features of mineralocorticoid excess, including marked hypokalemia and mild metabolic alkalosis, and an adrenal gland tumor was identified via abdominal ultrasonography. Serum aldosterone was undetectable, however. The markedly high serum deoxycorticosterone concentrations were speculated to have caused the clinical signs because in humans, deoxycorticosterone-producing tumors are associated with clinical signs of mineralocorticoid excess.[11] Serum deoxycorticosterone concentrations were not measured in the dog reported here. Because deoxycorticosterone is a precursor of corticosterone in the adrenal cortex,[20] it is possible that deoxycorticosterone was also present in excess. Corticosterone also possesses minimal mineralocorticoid activity. In relation to cortisol, corticosterone, deoxycorticosterone, and aldosterone have 15, 100-, and 3,000 times as much mineralocorticoid activity, respectively.[20] Because serum corticosterone concentrations were approximately 1,000 times as great as serum aldosterone concentrations, the relative contribution of serum corticosterone, deoxycorticosterone, or aldosterone concentrations to the clinical signs of mineralocorticoid excess was unknown.

In the dog reported here, the clinical signs, osteoporosis, and high serum ALP activity were strongly suggestive of glucocorticoid excess. Results of 2 ACTH stimulation tests indicated a subnormal serum cortisol response. Abdominal ultrasonography revealed an adrenal gland tumor. This finding, along with the suppression of serum cortisol, absence of a history of exogenous glucocorticoid administration, and plasma eACTH concentration below the reference range, was suggestive of excess adrenal gland secretion of a glucocorticoid other than cortisol. Dogs with adrenal gland tumors unresponsive to ACTH stimulation have been reported.[8,21] Although it has been suggested that lack of response of an adrenal gland tumor to exogenous ACTH may be attributable to lack of ACTH receptors,[22] this seems unlikely in the dog reported here because corticosterone and aldosterone increased greatly in response to an ACTH injection.

In humans, secretion of hormones other than cortisol from adrenocortical carcinomas is well documented.[3] We hypothesized that corticosterone was being produced in excess in the dog of this report. Corticosterone inhibits ACTH secretion.[23,24] In addition, because corticosterone is a precursor of aldosterone, excess corticosterone production could also explain the high serum aldosterone concentration. Accordingly, we investigated serum corticosterone and detected extremely high concentrations, compared with clinically normal dogs and dogs with classic HAC and hypercortisolemia. Interestingly, corticosterone secretion by adrenocortical carcinoma has been reported in humans, but aldosterone secretion was suppressed in those patients.[25]

Recently, excessive sex hormone production by an adrenocortical tumor was reported in 2 dogs. Clinical signs were suggestive of hypercortisolemia; however, ACTH stimulation testing detected a subnormal serum cortisol response to ACTH, and plasma eACTH concentration was low. The tumors produced estradiol, progesterone, and 17α-hydroxyprogesterone in both dogs and androstenedione as well in 1 dog. Serum

corticosterone concentration was not measured.[7] We did not measure sex hormone production by the tumor in the dog of this report, but it is possible that sex hormones also were produced.

Despite having serum cortisol concentrations less than reference range after ACTH administration, the dog had inadequate suppression after high-dose dexamethasone administration. It is possible that if cortisol production did not fluctuate according to the dog's physiologic requirements, total daily production of cortisol was inappropriately high despite resting cortisol concentration within reference range and lack of response to ACTH.[7] However, during mitotane treatment of HAC, a good clinical response is obtained if cortisol concentrations are reduced to concentrations similar to those detected in this dog.[7] It is possible that the adrenal gland tumor was secreting cortisol in small amounts, and such secretion would be expected to be resistant to dexamethasone suppression.[26] If a low-dose dexamethasone suppression test had been performed as the screening test in the dog of this report to diagnose HAC, a correct diagnosis of HAC would likely have been made. However, it would have appeared that the disease was attributable to excess cortisol secretion, and the abnormality in corticosterone secretion would have not have been detected.

Interestingly, the dog developed calcinosis cutis approximately 35 days after hormonal secretion by the tumor had been controlled by mitotane administration. Calcinosis cutis is characterized by dystrophic calcium deposition. The mechanisms are not completely understood but involve deposition of crystalline aggregates in dermal collagen.[17] Although it is possible that the tumor was secreting a hormone other than corticosterone and that caused the initial clinical signs and the calcinosis cutis, this seems unlikely given that secretion of corticosterone, cortisol, and aldosterone had decreased greatly. Because dermal complications of HAC may not resolve for months after control has been achieved, it is more likely that the calcinosis cutis was a result of damage to the skin that occurred before control was achieved.

Although production of hormones other than cortisol by an adrenocortical tumor seems to be rare, ultrasonographic examination of the adrenal glands is warranted in a dog that has clinical signs of HAC, a subnormal serum cortisol response on an ACTH stimulation test, and no history of exogenous glucocorticoid administration. Similarly, in dogs with signs of hyperaldosteronemia, further investigation of the adrenal glands is warranted.

a. Cortrosyn, Organon Inc, West Orange, NJ.
b. Coat-A-Count cortisol assay, Diagnostic Products Corp, Los Angeles, Calif.
c. ACTH assay, Nichols Institute, San Clemente, Calif.
d. Endocrine Section, Diagnostic Center for Population and Animal Health, Michigan State University, East Lansing, Mich.
e. Coat-A-Count aldosterone assay, Diagnostic Products Corp, Los Angeles, Calif.
f. Coat-A-Count rat corticosterone assay, Diagnostic Products Corp, Los Angeles, Calif.

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