Hyperadrenocorticism associated with excessive sex hormone production by an adrenocortical tumor in two dogs

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A 11-year-old spayed female Labrador Retriever weighing 32 kg (70.4 lb) was referred to Purdue University Veterinary Teaching Hospital (PUVTH) for evaluation of suspected hyperadrenocorticism (HAC). Clinical signs included polyphagia, polydipsia, and polyuria. Water consumption was variable but had been as high as 19 L (590 ml/kg of body weight)/d. Changes in coat color, weight gain, increased panting, and abdominal enlargement were also reported.

Abnormalities noticed during physical examination were limited to a coarse coat and a pendulous abdomen. Rectal temperature was 101.8 F (38.8 C), heart rate was 86 beats/min, and the dog was panting.

Results of a CBC revealed mild lymphopenia (0.78 X 10³ cells/µl; reference range, 1 to 5 X 10³ cells/µl). Serum biochemical abnormalities included mild hypernatremia (149 mmol/L; reference range, 138 to 148 mmol/L), high total CO₂ (28 mmol/L; reference range, 13 to 24 mmol/L), and moderately high alkaline phosphatase activity (1,001 U/L; reference range, 20 to 137 U/L). Thyroxine concentration was 2.0 µg/dl (reference range, 1.3 to 4.0 µg/dl). A urine sample collected by cystocentesis had a specific gravity of 1.004 but was otherwise unremarkable. The urine protein-to-creatinine ratio was within reference range (23; reference range, 8 to 24). Endogenous ACTH concentration was low (1.7 pmol/L; reference range, 6.7 to 25.0 pmol/L).

Adrenalectomy was recommended but was declined by the owners because of the cost and the risk of perioperative mortality. Aliquots of serum obtained before and after ACTH administration were submitted to the University of Tennessee for measurement of adrenal sex hormone concentrations. Validation of these assays and determination of sex-dependent reference ranges have been reported elsewhere. Increased concentrations of estradiol, progesterone, and 17-hydroxyprogesterone were identified (basal estradiol = 38.4 pg/ml, reference range, 28 to 53 pg/ml; poststimulation estradiol = 84.3 pg/ml, reference range, 26 to 51 pg/ml; basal progesterone = 2.8 ng/ml, reference range, < 0.2 ng/ml; poststimulation progesterone = 2.7 ng/ml, reference range, 0.4 to 1.1 ng/ml; basal 17-hydroxyprogesterone = 2.3 ng/ml, reference range, < 0.4 ng/ml; poststimulation 17-hydroxyprogesterone = 2.0 ng/ml, reference range, 0.3 to 1.5 ng/ml). Treatment was initiated with the adrenolytic drug mitotane (750 mg, q12 h, PO; 47 mg/kg [21.36 mg/lb] total daily dose). Prednisone (0.25 mg/kg [0.11 mg/lb] q 24 h, PO) was administered concomitantly.

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Following 10 days of treatment, the dog was reexamined. No improvement in clinical signs was evident to the owner, and physical examination findings were unchanged. An ACTH stimulation test was performed and revealed no change in the cortisol response to ACTH (basal cortisol = 1.8 µg/dl; poststimulation cortisol = 2.1 µg/dl). Mitotane was continued at the same dose for another 10 days, after which there was still no clinical improvement. Radiography of the abdomen revealed an increase in the size of the left adrenal mass. There was no evidence of metastatic disease or invasion of the vena cava. An ACTH stimulation test was again performed (basal cortisol = 2.0 µg/dl; poststimulation cortisol = 1.5 µg/dl), and prestimulation adrenal sex hormone concentrations were measured. Concentrations of progesterone, testosterone, dihydroepiandrosterone sulfate (DHEAS) and 17-hydroxyprogesterone were all considerably higher than reference ranges and had increased from pretreatment values (basal progesterone = 17.9 ng/ml; reference range, < 0.2 ng/ml; basal testosterone = 3.0 ng/ml; reference range, 0.1 to 0.4 ng/ml; basal DHEAS = 53.2 µg/dl; reference range, 0.3 to 12 ng/ml; basal 17-hydroxyprogesterone = 6.8 ng/ml; reference range, < 0.4 ng/ml). The owners declined any further treatment. The dog died unexpectedly 2 months later. At necropsy, a bilobulated mass measuring approximately 10 × 10 × 3.75 cm effaced the left adrenal gland. A thick and well-organized fibrous connective tissue capsule covered the mass, and there were multiple fibrous adhesions involving the pancreas and the serosal surfaces of the small and large intestines. The parenchyma of the mass was friable and pale white. The right adrenal gland measured approximately 1.2 × 1.0 cm in its greatest dimensions. The pituitary gland was grossly normal. Microscopic examination of the left adrenal gland mass revealed adrenocortical carcinoma. Small nests of adrenocortical neoplastic cells were present within a delicate fibrovascular stroma. Neoplastic cells were polyhedral with abundant amounts of pale eosinophilic cytoplasm with large oval vesicular nuclei. Cellular atypia, anisocytosis, and anisokaryosis were commonly observed. Much of the mass was necrotic and contained large amounts of fibrin and extravasated erythrocytes. The right adrenal gland was histologically normal. Tissue section of an embolus from the valve of the caudal vena cava near the mass contained low numbers of adrenocortical neoplastic cells, similar to those observed in the adrenocortical carcinoma. The embolus also contained mineralized fibrin and cellular debris adherent to the neoplastic cells.

A 9-year-old castrated male miniature Poodle weighing 5.9 kg (12.98 lb) was referred to PUVTH for evaluation of suspected HAC. Clinical signs reported by the owner included polyuria, polydipsia, and polyphagia. Results of an ACTH stimulation test performed by the referring veterinarian revealed a subnormal cortisol response to ACTH (basal cortisol concentration = 3.0 µg/dl; reference range, 1.0 to 6.0 µg/dl; 1 hour poststimulation cortisol concentration = 3.6 µg/dl; reference range, 7.0 to 17.0 µg/dl). On physical examination, the dog was obese, heart rate was 92 beats/min with an irregular rhythm, respiratory rate was 32 breaths/min, and rectal temperature was 38.3 C (100.9 F). An ECG revealed an irregular rhythm, a wandering atrial pacemaker, and occasional second degree AV block.

Hematologic abnormalities included polycythemia (Hct, 68.2%; reference range, 37 to 55%), mature neutrophilia (19.62 × 10³ cells/µl; reference range, 3 to 12 × 10³ cells/µl), lymphopenia (0.84 × 10³ cells/µl; reference range, 1.0 to 5.0 × 10³ cells/µl), and eosinopenia (0; reference range, 0.1 to 1.25 × 10³ cells). Serum biochemical analysis was unremarkable with the exception of mild increases in alanine transaminase (99 U/L; reference range, 3 to 69 U/L) and alkaline phosphatase (238 U/L; reference range, 20 to 157 U/L) activities and cholesterol (713 mg/dl; reference range, 125 to 301 mg/dl) concentration. Urinalysis revealed a specific gravity of 1.018 and benign sediment.

Mild hepatomegaly was evident radiographically. Ultrasound examination of the abdomen revealed an enlarged and irregularly margined right adrenal gland measuring 1.26 cm across its short axis. No invasion of the vena cava was evident. The dimensions of the left adrenal gland were normal. The liver was hyperechoic, compared with the spleen, and had a mottled echogenicity. Thoracic radiography was unremarkable. Cardiac ultrasound revealed mild left ventricular hypertrophy. Noninvasive systolic blood pressure measurements, using a Doppler technique, were made repeatedly and ranged from 140 to 180 mm Hg.

Endogenous ACTH concentration was low (1.4 pmol/L; reference range, 6.7 to 25.0 pmol/L). An ACTH stimulation test was repeated with measurement of adrenal sex hormones, as described. Concentrations of androstenedione, estradiol, progesterone, and 17-hydroxyprogesterone were considerably increased before and after administration of ACTH (basal androstenedione = 24.7 ng/ml; reference range, 2.7 to 8.0 ng/ml; poststimulation androstenedione = 83.7 ng/ml; reference range, 3.0 to 10.0 ng/ml; basal estradiol = 80.7 µg/ml; reference range, 28 to 63 µg/ml; poststimulation estradiol = 79.1 µg/ml; reference range, 30 to 69 µg/ml; basal progesterone = 2.1 ng/ml; reference range, < 0.1 ng/ml; poststimulation progesterone = 16.1 ng/ml; reference range, < 1.2 ng/ml; basal 17-hydroxyprogesterone = 0.9 ng/ml; reference range, < 0.1 ng/ml; poststimulation 17-hydroxyprogesterone = 16.4 ng/ml; reference range, 0.4 to 1.2 ng/ml). Basal testosterone concentration was within reference range but was increased above reference range after ACTH administration (0.97 ng/ml; reference range, 0.3 to 0.6 ng/ml).

One week later, the right adrenal mass was removed via a standard midline celiotomy. Gross extension of the mass into surrounding structures was not apparent. The left adrenal gland appeared small. Intraoperative complications were not encountered, and the dog recovered without complications. During the immediate postoperative period, hydrocortisone was administered as a continuous IV infusion (0.65 mg/kg/h [0.295 mg/lb/h]). A tapering dose of prednisone was substituted once the dog tolerated medicament orally (0.4 mg/kg [0.18 mg/lb]). PO for 5 days, then 0.4 mg/kg [0.18 mg/lb], PO, q 24 h for 5 days,
then 0.4 mg/kg (0.18 mg/lb), PO, q 48 h for 30 days). Histologic examination of the excised right adrenal mass was consistent with adenocortical carcinoma. The neoplastic cells were round to polygonal mononuclear cells with abundant pale foamy basophilic cytoplasm and mild to moderate nuclear polymorphism. The mass invaded through the thin fibrous capsule of the adrenal gland. Also evident within the mass were multiple foci of extramedullary hematopoiesis, predominantly erythropoiesis.

The dog was reexamined 2 months after surgery. No prednisone had been administered for 21 days. The owners reported resolution of the dog's polyuria and polydipsia. On physical examination, the dog was slightly obese and had mild seborrhea. Results of a CBC were unremarkable with resolution of the previously noted polycythemia; the only abnormalities evident in the serum biochemical analysis were mild increases in cholesterol (358 mg/dl; reference range, 125 to 301 mg/dl) and total CO₂ (28 mmol/L; reference range, 13 to 24 mmol/L) concentrations. An ACTH stimulation test was performed. The adrenal sex hormone concentrations had decreased to within reference ranges, and the post-stimulation cortisol concentrations had increased such that there was now an appropriate response to ACTH administration. The other measured adrenal hormone concentrations were also within reference ranges. Thirteen months after surgery the dog was clinically normal. Thoracic radiography and abdominal ultrasonography revealed no evidence of metastatic disease.

Hyperadrenocorticism is defined as increased production of steroid hormones by the adrenal cortex. The term is usually associated with abnormal glucocorticoid production, a syndrome that is well described in dogs. However, HAC may also cause excessive secretion of mineralocorticoids and sex hormones by the adrenal cortex. Hyperadrenocorticism caused by excessive production of mineralocorticoids results in hypokalemia and hypertension. Synthesis of the mineralocorticoid hormone deoxycorticosterone by an adrenal tumor has been reported in a dog. Findings in the 2 dogs reported here illustrate the clinical and pathologic findings that result from HAC associated with excessive sex-hormone production. This syndrome has been described in humans, cats, and ferrets.

Both the dogs of this report had clinical signs suggestive of excessive glucocorticoid production, including polyuria, polydipsia, and polyphagia. The discovery of an adrenal mass in both dogs appeared initially to support adrenal dependent HAC causing excessive production of glucocorticoids. However, cortisol concentrations were below reference range in both dogs following ACTH administration. Iatrogenic HAC attributable to exogenous corticosteroid administration could have accounted for the clinical signs and the low measured cortisol concentrations but not the presence of the adrenal masses. No source of exogenous glucocorticoid could be identified in either dog.

A nonfunctional adrenal tumor was considered unlikely, because the dogs had clinical signs that could not be explained by the presence of a nonfunctional mass, and because cortisol concentrations were low following ACTH administration. A unilateral nonsecre-
direct glucocorticoid effects, high progesterone concentrations may result in clinical signs of disease by displacing cortisol from cortisol binding protein.13 This results in high concentrations of free cortisol even though the total serum cortisol concentration is decreased. Because it is the free or unbound cortisol that is active and able to exert its effects on a variety of tissues, clinical signs of cortisol excess may develop. Administration of progesterone to dogs results in profound suppression of the hypothalamic-pituitary adrenal axis.14 Thus, elevation of progesterone concentration over a prolonged period would be expected to result in decreased endogenous ACTH concentrations and a decreased response to ACTH administration, as was evident in both the dogs reported here.

Progesterones (progesterone and 17-hydroxyprogesterone) are synthesized in the adrenal cortex from cholesterol via the intermediaries pregnenolone and 17-hydroxyprogrenolone. However, only small amounts of progesterone are normally secreted into the circulation, with most being converted to mineralocorticoids, glucocorticoids, or to androgens (DHEAS and androstenedione). It is these androgens that normally constitute the main sex hormone product of the adrenal glands. These androgens, in turn, are the substrates for testosterone and estrogen production by peripheral tissues. In humans with adrenocortical neoplasms, aberrant biosynthetic pathways have been well characterized.15 Adrenal gland neoplasms may be deficient in the enzymes involved in normal steroidogenic pathways, such as 21β-hydroxylase or 11β-hydroxylase. When such enzyme deficiencies develop, they cause accumulation of precursor steroids proximal to the blockade. These precursors may either be released and cause clinical signs directly or they may be shunted into other metabolic pathways, such as those for androgen biosynthesis, and result in clinical signs indirectly. Such enzyme deficiencies are most often due to adrenocortical adenocarcinoma. Tumors described as adrenocortical adenomas are rare, and it is thought that an inherited partial enzyme deficiency is present from birth but that it is clinically asymptomatic until the development of an adrenal tumor in later life.5

In both the dogs of this report, the tumors were characterized as adrenocortical carcinomas. Two cases of sex hormone producing adrenal tumors have been reported in cats; these tumors were also both described histologically as adrenocortical carcinomas.6,7 In humans, virilizing adrenal tumors are almost invariably carcinomas and have a high propensity to metastasize.8 Further work is required to characterize production of progesterone, 17-hydroxyprogesterone, and DHEAS in dogs with benign versus malignant adrenal tumors. Studies suggest that adrenal sex hormones are also increased in dogs with pituitary dependent hyperadrenocorticism.9,10

The Labrador Retriever of this report was treated with mitotane because the owners declined surgery. Mitotane causes selective progressive necrosis of the adrenal cortex and has been found to be an acceptable alternative to surgery in many dogs with cortisol secreting adrenocortical tumors, with 60% of dogs treated having a good to excellent response.11 The finding of extensive necrosis of the adrenal gland in this dog may represent a partial response to mitotane treatment, although necrosis occurs commonly in large adrenocortical carcinomas even without treatment. In general, dogs with adrenocortical neoplasia require a high dose of mitotane for remission of clinical signs.12 It is possible that this dog would have responded to a higher dose of mitotane than it received, but the owners were discouraged by the continued growth of the tumor and further increase in sex hormone concentrations and refused additional treatment.

References