



LAB REPORT This rare case of adrenal-dependent AHAC provides evidence that trilostane therapy may effectively manage associated clinical signs if surgical intervention is not pursued.

CASE REPORT: ENDOCRINOLOGY

Adrenal-Dependent Atypical Hyperadrenocorticism

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Spontaneous canine hyperadrenocorticism (HAC), also referred to as Cushing's syndrome, is one of the most frequently diagnosed endocrinopathies in small animal practice. The syndrome reflects prolonged exposure to excessive amounts of glucocorticoids. Dogs with HAC generally exhibit polyuria, polydipsia, polyphagia, a pot-bellied appearance, and decreased fur coat quality. A clinical suspicion of HAC is supported by laboratory findings associated with hypercortisolemia, such as increased alkaline phosphatase (ALP) activity, hypercholesterolemia, thrombocytosis, and proteinuria.^{1,2}

Estimated prevalence of HAC is 0.2%.³ For most patients, the underlying disorder is a pituitary tumor releasing inappropriate amounts of adrenocorticotropic hormone (ACTH); this disorder is referred to as pituitary-dependent HAC and is associated with bilateral adrenomegaly. Other patients have adrenal-dependent HAC, in which an adrenal cortical tumor autonomously produces glucocorticoids.⁴ Most patients

exhibiting signs of spontaneous HAC have excessive cortisol levels, and the terms "HAC" and "hypercortisolemia" are used interchangeably. Therefore, standard diagnostic tests for HAC (e.g., low-dose dexamethasone suppression test, ACTH stimulation test, and urine cortisol:creatinine ratio) rely on measurement of cortisol.²

Infrequently reported are dogs that display a cushingoid phenotype but secrete cortisol at either normal or subnormal levels. For some of these individuals, increased concentrations of various cortisol precursors (e.g., 17-hydroxyprogesterone and androstenedione) have been reported and it is hypothesized that these steroids interact with glucocorticoid receptors and cause the clinical signs traditionally associated with hypercortisolemia.⁵⁻⁸ The term "atypical HAC" (AHAC) describes this syndrome and is best defined by cushingoid signs in the absence of documented hypercortisolemia. Because increased concentrations of various cortisol precursors in dogs with both

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hypercortisolemia and nonadrenal disorders have been reported, the actual pathogenesis of AHAC remains unclear.⁹ Previous reports have described AHAC associated with an adrenal tumor and clinical signs that resolved after adrenalectomy.¹⁰ Also reported is clinical improvement in dogs with AHAC after medical therapy with either trilostane or mitotane.^{5,8,11}

The recommended treatment for HAC is based primarily on the underlying cause. For pituitary-dependent HAC, the primary treatment is medical management with either trilostane or mitotane.^{12,13} Trilostane inhibits an enzyme needed for the synthesis of cortisol; it is licensed for the treatment of both forms of HAC in dogs and is generally well tolerated. Mitotane induces irreversible adrenal necrosis; it is not approved for use in dogs, and the dose must be carefully titrated. For dogs with adrenal-dependent HAC and no metastatic disease, adrenalectomy is considered the treatment of choice and may be curative. Removal of the affected gland also prevents complications such as rupture or vascular invasion with thrombosis.¹⁴ However, for dogs that are poor surgical candidates or that have other considerations that preclude adrenalectomy, medical therapy may be prescribed. Therapeutic recommendations for cases of AHAC mirror those for typical HAC in that adrenalectomy is the treatment of choice for functional adrenal neoplasms and medical management is used for pituitary-dependent disease.

This case report describes the case of a Labrador retriever with adrenal-dependent AHAC that was clinically well-managed with trilostane.

THE CASE

The patient was a 9-year-old, castrated male Labrador retriever. For several months before the dog's presentation to the Texas A&M University Veterinary Medical Teaching Hospital (TAMU VMTH) in late April 2020, the client noted that the dog seemed restless, characterized by pacing at night and persistent panting. Initially, this behavior was presumed to be a manifestation of discomfort secondary to osteoarthritis, but various analgesic treatments (tramadol, nonsteroidal anti-inflammatory drugs, gabapentin) did not alleviate the clinical signs. The client also reported that the dog was polydipsic and had recently started waking her up in the middle of the night to urinate. After having been groomed 12 months earlier, the patient's

fur failed to adequately grow back, and recently, patches of alopecia started to appear over his body.

Multiple urinalyses performed within 18 months of presentation revealed hyposthenuria, with specific gravities ranging from 1.005 to 1.006, but no proteinuria. Mild hypokalemia was also identified, with values ranging from 3 to 3.1 mmol/L (reference range [RR] 3.5 to 5.8 mmol/L). No elevations in ALP activity were observed and the platelet count was within the reference range. Months before presentation, levothyroxine therapy was initiated due to a subnormal serum thyroid concentration (0.9 µg/dL; RR 1 to 4), but this therapy was discontinued approximately 1 month later because of a perceived worsening of the

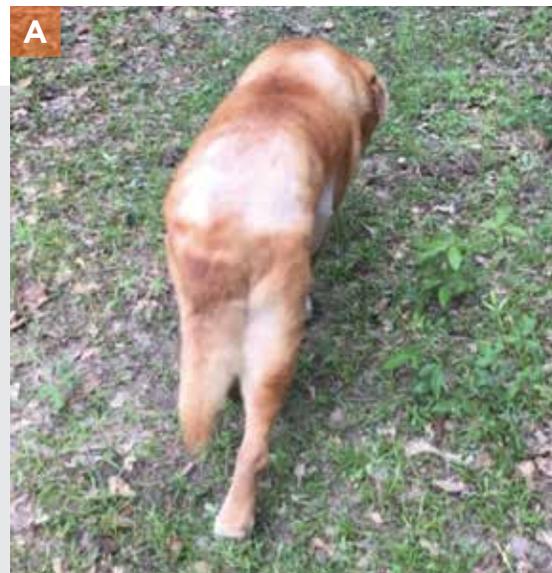


FIGURE 1. The patient's fur coat at the time of diagnosis. **(A)** Overall quality was poor, with large areas of alopecia along the dorsal tail base, neck, and caudal scapula regions. **(B)** Although emphasized by the clipping performed before ultrasonography, a large pendulous abdomen can be appreciated.



patient's clinical state and a substantially elevated post-pill total thyroid level (5.9 $\mu\text{g/dL}$). Thoracic radiographs raised concern for either a dilated aorta or a potential heart-base mass; 2 days later, the patient was referred to the TAMU VMTH Cardiology Service.

Physical Examination

At presentation to TAMU VMTH, the patient had a pendulous, distended abdomen and multiple patches of alopecia (dorsal tail base, dorsal cervical and scapular regions). The general coat quality was poor (FIGURE 1). The patient was considered to be overweight; body condition score (BCS) was 7/9. Persistent panting without stridor and mild muscle wasting on the hindlimbs were noted.

Noninvasive blood pressure measurement (Doppler) identified severe systemic hypertension (220 to 250 mm Hg systolic), and a fundic examination identified punctate retinal hemorrhages bilaterally consistent with

a hypertensive retinopathy. No other abnormalities were noted.

Diagnostic Tests and Results

Repeated thoracic radiographs showed widening of the cranial mediastinum and an enlarged aortic arch, considered secondary to systemic hypertension (FIGURE 2). Echocardiographic findings were also consistent with systemic hypertension, identifying trace aortic insufficiency and aortic dilation. Abdominal ultrasonography identified a markedly enlarged and globoid left adrenal gland (39 \times 51 mm) with evidence of invasion of the adjacent caudal vena cava (FIGURE 3). The right adrenal gland was an appropriate shape with a caudal pole width of 5.5 mm. In light of this dog's systemic hypertension, differential diagnoses for the adrenal tumor included a cortical tumor secreting cortisol plus/minus aldosterone or a pheochromocytoma. Because the history and physical examination findings were most suggestive of abnormal adrenal cortical function, this possibility was prioritized.

An ACTH stimulation test using cosyntropin at a dose of 1 $\mu\text{g/kg}$ IV was performed. Baseline and 1-hour post-ACTH serum samples were submitted for the measurement of cortisol, androstenedione, estradiol, progesterone, 17-hydroxyprogesterone, and testosterone (University of Tennessee College of Veterinary Medicine, vetmed.tennessee.edu/vmc/dls/endocrinology). Serum aldosterone was also measured at 1 hour after ACTH administration (Michigan State Veterinary Diagnostic Laboratory, cvm.msu.edu/vdl) (TABLE 1). The cortisol response to ACTH stimulation was blunted; the baseline value was 3.1 $\mu\text{g/dL}$ (RR <1

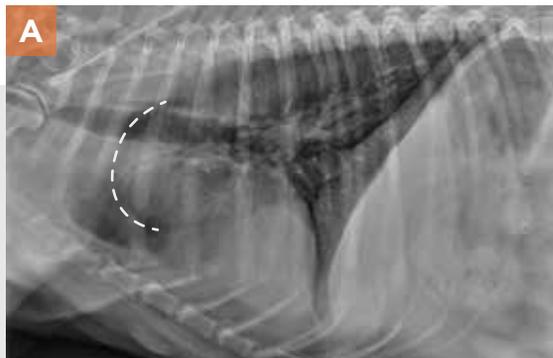


FIGURE 2. Thoracic radiographs showing (A) an enlarged aorta (dashed line) and (B) a focally widened cranial mediastinum (arrows).



FIGURE 3. Left adrenal gland, showing abnormal shape and measuring approximately 39 \times 51 mm (outlined by Xs).

TABLE 1 Results of Extended Adrenal Function Testing After IV Injection of Cosyntropin at 1 µg/kg

| HORMONE | BASELINE | BASELINE REFERENCE RANGE | 1 HOUR AFTER ACTH | REFERENCE RANGE AFTER ACTH |
|------------------------|-------------------|--------------------------|-------------------|----------------------------|
| Cortisol, µg/dL | 3.1 | <1-5.6 | 4.3* | 7.1-15.1 |
| Androstenedione, ng/mL | 4.4 [†] | 0.05-0.36 | >10 [†] | 0.24-2.9 |
| Estradiol, pg/mL | 58.6 | 23.1-65.1 | 64.2 | 23.3-69.4 |
| Progesterone, ng/mL | 0.27 [†] | <0.2 | 0.9 | 0.22-1.45 |
| 17-OHP, ng/mL | 0.72 [†] | 0.08-0.22 | 2.57 | 0.25-2.63 |
| Testosterone, ng/dL | <15 | <15-24 | <15 | < 15-42 |
| Aldosterone, pmol/L | 143 | 14-957 | 278 | 197-2103 |

ACTH=adrenocorticotrophic hormone; 17-OHP=17-hydroxyprogesterone
[†]Below the reference range
^{*}Above the reference range

to 5.6) and the post-ACTH value was 4.3 µg/dL (RR 7.1 to 5.1). The baseline and poststimulation androstenedione concentrations were markedly elevated; the baseline was more than 10 times the upper limit of the reference range (4.4 ng/mL [RR 0.05 to 0.36]), and the poststimulation value was too high to measure (>10 ng/mL [RR 0.24 to 2.9]).

Testing for a pheochromocytoma with a urine metanephrine:creatinine ratio (UMCR) was not performed at this time. Although this test may reliably identify dogs with a pheochromocytoma, many dogs with HAC are reported to have an increased UMCR. This test is therefore less discriminatory in dogs with Cushing’s syndrome and results should be interpreted with caution.¹⁵

Treatment

To address the patient’s hypertension while awaiting results of the adrenal function tests, amlodipine besylate was prescribed at 0.2 mg/kg PO q12h. Unilateral adrenalectomy was discussed with the client, who declined out of concern for risk and cost. After review of the hormone test results, trilostane (Vetoryl; Dechra, dechra-us.com) was prescribed at 1.2 mg/kg PO q12h.

Outcome

Blood pressure rechecked 12 hours after amlodipine administration showed significant reduction in systolic pressure. However, within a week of starting this medication and before starting trilostane, severe peripheral edema, a rare side effect of amlodipine in dogs,¹⁶ developed and was managed with a 50% reduction in dose. This reduction led to resolution of the edema and adequate control of the hypertension

(average systolic blood pressure 145 mm Hg) within 3 weeks. The positive response to amlodipine made a pheochromocytoma unlikely, so UMCR testing was not performed for this patient.

After approximately 1 month of trilostane therapy, the client reported significant improvement in the dog’s status, with less pacing and panting at night and decreased polyuria and polydipsia. After 4 months of trilostane therapy, recheck serum chemistry documented a persistent mild hypokalemia (3.1 mmol/L [RR 3.5 to 5.8]), but potassium supplementation was withheld due to potential alterations in potassium handling secondary to trilostane administration. ACTH stimulation tests are routinely used to monitor dogs receiving trilostane therapy, although target post-ACTH cortisol concentrations are controversial.^{13,17} Because this dog’s cortisol secretion was subnormal at the time of diagnosis, the decision was made to not measure either baseline or post-ACTH cortisol again, as long as the dog was clinically well. An ACTH stimulation test



FIGURE 4. Improved fur coat quality after 7 months of trilostane administration.

Photo courtesy Kim Newsome



would certainly be indicated if the dog were to show any signs of hypocortisolemia.

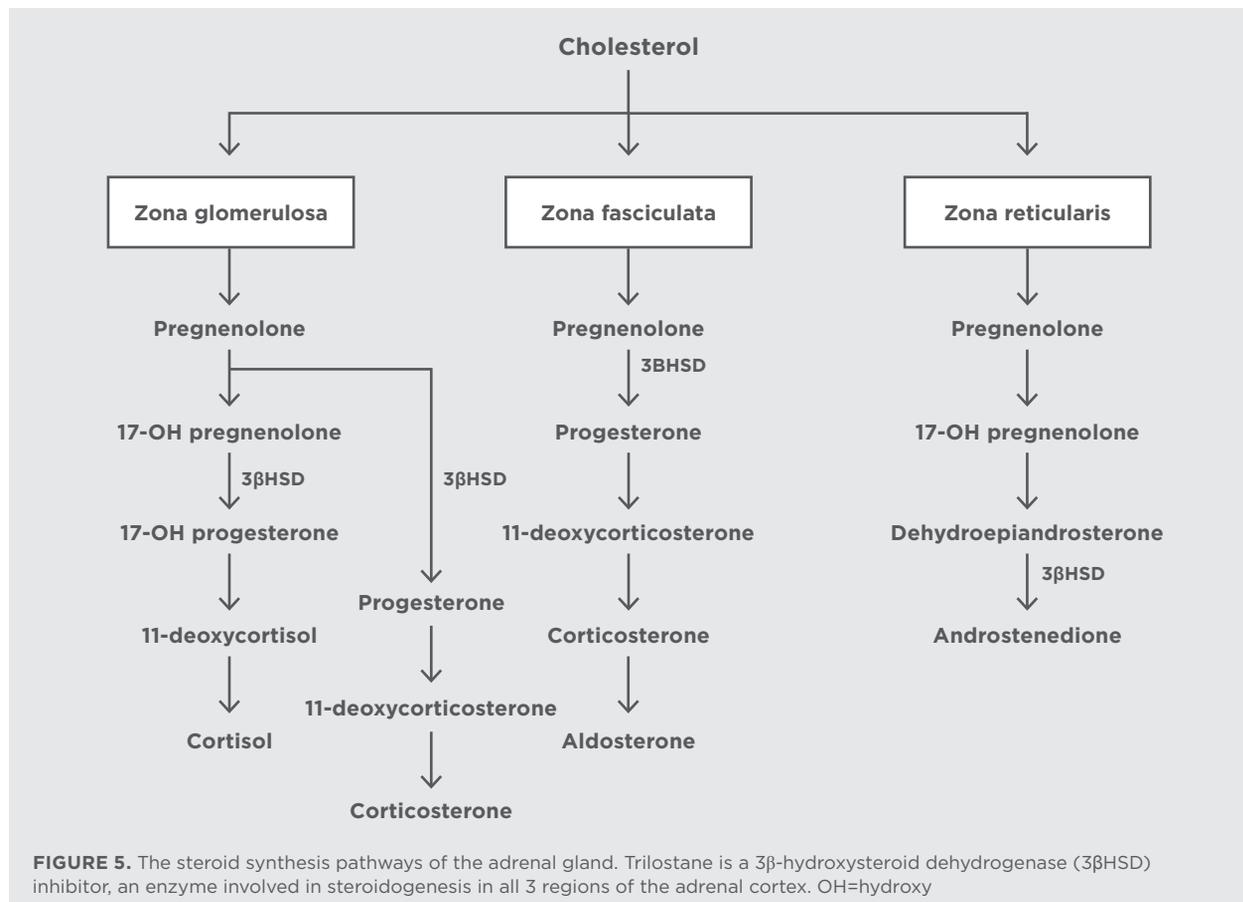
Over the next 5 months, the client appreciated an improvement in coat quality and growth of new hair in the alopecic areas (FIGURE 4). In addition, the pot-bellied appearance resolved and the dog's muscle mass improved. The client has not noticed any signs associated with hypoadrenocorticism (lethargy, vomiting, diarrhea, or inappetence). At 13 months after initial diagnosis, the dog is reportedly still doing well at home and receiving the same dose of trilostane.

DISCUSSION

For most patients with HAC, the cushingoid signs are secondary to hypercortisolism, although numerous reports have documented concurrent increases in cortisol precursor concentrations. However, several case reports describe patients with cushingoid signs, such as the patient reported here, in which cortisol secretion is within normal limits or is suppressed and steroid precursor concentrations are elevated.^{5,6,8,18,19} For this

patient, extended adrenal function testing was recommended due to the presence of an adrenal mass and the normal ALP activity.²⁰ The persistent hypokalemia remains unexplained but may reflect an interaction between androstenedione (or other unmeasured steroid precursors) and either mineralocorticoid receptors or endogenous mineralocorticoid activity.^{21,22}

Trilostane is a 3β -hydroxysteroid dehydrogenase inhibitor (FIGURE 5) and one of the most commonly used medical therapies for dogs with pituitary-dependent HAC.²³ In addition, trilostane has been shown to be effective in dogs with hypercortisolemia resulting from functional adrenal tumors.²⁴ Of note, androstenedione concentrations are apparently unaffected by trilostane administration.²⁵ In humans, this drug is known to modulate the interaction of estrogen with its receptor and is used for this purpose in women with tamoxifen-resistant breast cancer.²⁶ In rats, trilostane administration has been shown to down-regulate mRNA for glucocorticoid receptors.²⁷ Decreased receptor function or expression in target



organs could mitigate the effects of steroid hormones even if serum concentrations remain unaffected, but no current evidence supports this hypothesis for dogs.

This rare case of adrenal-dependent AHAC provides evidence that trilostane therapy may effectively manage associated clinical signs and improve quality of life if surgical intervention is not pursued. However, the clinical response cannot be predicted, and clients must be warned about the risks of iatrogenic hypoadrenocorticism. **TVP**

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Disclosure

Dr. Cook has received honoraria from Dechra Veterinary Products for past projects.