



ATYPICAL HYPERADRENOCORTICISM

Case Report
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Signalment:

“Bailey”
Adult FS English Bulldog

History:

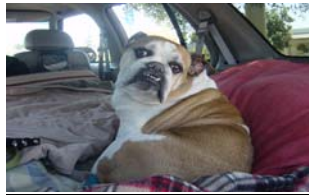
Bailey initially presented to the VMSG emergency service for respiratory distress. She had an uncomplicated surgical excision of a left arytenoid mass and soft palate resection. Histopathology of the mass revealed inflammation and marked granulation tissue. The owners reported that since adopting Bailey two months prior to presentation, she had always been polyuric and polydipsic with an excellent appetite. Past medical problems included chronic contact dermatitis and osteoarthritis. Pre-anesthetic blood panel showed numerous abnormalities (see below) and she was transferred to the internal medicine service for further diagnostics.

Clinical Exam:

Bailey had corneal neovascularization and severe scleral hyperemia OD and the fundus was not visible due to the presence of red/gray opacity in the posterior segment. There was a previously documented mammary gland nodule (the owner had declined excisional biopsy). Bailey was referred to a veterinary ophthalmologist for her ocular changes and a presumptive diagnosis of hypertensive retinopathy was made (retinal detachment OD and focal retinal edema OS), although other inflammatory etiologies could not be completely ruled out. Doppler systolic arterial blood pressure was measured on a couple different occasions, and all times measured high normal.

Diagnostic Imaging:

Pre-anesthetic thoracic radiographs and abdominal ultrasound were unremarkable.



Laboratory Data:

Pre-anesthetic blood panel results showed: elevated ALP (336 U/L), hypercholesterolemia (592 mg/dL), and hypoalbuminemia (1.7 g/dL). Urinalysis results showed isosthenuria (USG 1.015) with 3+ proteinuria and urine culture grew *E.coli* that was treated with antibiotics. Two weeks later, a urine culture was negative for growth and urine protein/creatinine ratio (8.3) was consistent with moderate proteinuria. Serum *Coccidioides immitis* titer and heartworm antigen test were negative. A low dose dexamethasone suppression test (LDDST) was normal. Diagnostic work-up for atypical hyperadrenocorticism was pursued with a University of Tennessee ACTH Stimulation Adrenal Panel (which measures pre and post ACTH stimulation cortisol, androstenedione, estradiol, progesterone, 17 OH progesterone, and aldosterone levels). Results showed elevated levels of estradiol and progesterone pre-ACTH stimulation and elevated levels of androstenedione, estradiol, progesterone, and 17 OH progesterone post-ACTH stimulation.

Diagnosis:

- * Pituitary-dependent atypical hyperadrenocorticism
- * Glomerulopathy – idiopathic or secondary to untreated hyperadrenocorticism
- * Presumptive hypertensive retinopathy – possibly episodic or previous hypertension due to untreated hyperadrenocorticism and/or glomerulopathy

Treatment/Management:

For her ocular disease, topical prednisolone acetate OD was prescribed (to treat secondary inflammation induced by intra-ocular bleeding). For the proteinuria, she was treated with oral enalapril, low dose aspirin, and Hill’s Prescription K/D diet. For her atypical Cushing’s disease, *low dose* Lysodren (mitotane) therapy was initiated with a divided BID dose (25 mg/kg/day) given for 4 days followed by a 2 day rest period and then continued with 25 mg/kg/wk maintenance therapy divided three times a week until otherwise directed.

Prognosis: Guarded to good with appropriate treatment .

Discussion:

Hyperadrenocorticism (HAC) is a clinical syndrome associated with various clinical signs and chemical abnormalities that result from chronic exposure to glucocorticoids (most notably, cortisol). With atypical HAC, patients may have the same constellation of clinical signs and laboratory abnormalities, however, they have a normal or subnormal cortisol response to the common adrenal function tests with elevations in other adrenocortical hormones (sex hormones, aldosterone). Approximately 85% of cases of naturally occurring HAC are caused by a pituitary tumor that produces excessive amounts of ACTH, stimulating the secretion of adrenocortical hormones. The remaining cases are caused by an adrenocortical adenoma or carcinoma that functions autonomously to secrete excessive amounts of adrenal steroids. Approximately 5% of dogs with Cushing's have atypical HAC, and these may be pituitary or adrenal-dependent. It has been suggested that dogs with atypical HAC could have several derangements in the adrenal steroid production pathway with relative deficiencies in some enzymes that are necessary for the production of cortisol. This may result in the accumulation of cortisol precursors that are shunted into other metabolic pathways, such as androgen biosynthesis. Some progestins have intrinsic glucocorticoid activity and this has been proposed as a potential cause of the clinical signs in dogs with atypical HAC. Another theory suggests that progestins may displace cortisol from cortisol-binding protein resulting in an excess of free cortisol (which is metabolically active) even though the total serum cortisol concentrations are normal or decreased.

Diagnosis of atypical HAC is similar in many respects to typical HAC. Diagnostic work-up includes a thorough history, physical exam, routine laboratory diagnostics, imaging, and adrenal function tests. The history commonly includes polyuria and polydipsia (85% of cases) and polyphagia (60-90% of cases) and these signs may precede others by weeks to months. Lethargy and excessive panting are also common complaints. Physical exam may reveal: a pendulous abdomen (70-90% of cases), bilaterally symmetrical alopecia with a dull hair coat, muscular weakness and atrophy, calcinosis cutis, keratin plugs, thin skin, hyperpigmentation, anestrus/testicular atrophy, or CNS signs. A CBC may reveal a stress leukogram and a chemistry panel may show elevated ALP (85-90% of cases), ALT, and hypercholesterolemia. Urinalysis results often reveal hyposthenuria or isosthenuria and proteinuria. About 50% of dogs with HAC will have a urinary tract infection and a urine culture is usually indicated. Abdominal radiographs may reveal mineralization of adrenal tumors (about 50% of cases) and/or hepatomegaly. Abdominal ultrasound findings consistent with pituitary dependent HAC include bilaterally normal adrenals, bilaterally symmetric/asymmetric adrenomegaly while unilateral adrenomegaly is expected in dogs with an adrenal tumor (unless they have bilateral adrenal tumors, which is rare). A low-dose dexamethasone suppression test (LDDST) and ACTH stimulation test that measure only cortisol are normal in a dog with atypical HAC. The test for diagnosing atypical HAC is an ACTH stimulation test that measures multiple adrenal steroids (progestins, androgens, glucocorticoids, and aldosterone). Frequently, dogs will have an elevation in progesterone and 17 OH progesterone, although elevations in these hormones have also been documented in dogs with non-adrenal illness. Therefore, the diagnosis of atypical HAC should only be made in conjunction with the aforementioned findings in the history, physical exam, routine laboratory test results and imaging studies.

The preferred treatment for atypical HAC may be Lysodren therapy as it effectively lowers cortisol, androstenedione, progesterone, and 17 OH progesterone levels (although estradiol is not always suppressed). It is an adrenocorticolytic agent with an induction dose that rapidly lowers hormone secretion from the adrenal cortex, and a maintenance dose that maintains more normal adrenal hormone secretion. With atypical HAC, lower doses of Lysodren are used (25 mg/kg/day for induction vs 50 mg/kg/day for typical Cushing's, and 25 mg/kg/wk for maintenance vs. 50 mg/kg/wk for typical Cushing's) with only a few days of induction (regardless of whether their excessive drinking improves or does not improve during this induction period) in order to reduce elevated steroid hormone levels without inducing hypocortisolemia. Trilostane therapy (although ideal for typical HAC), may not be optimal since it always increases 17 OH progesterone and frequently increases estradiol and androstenedione levels due to the adrenocortical enzymes that it inhibits. Other proposed treatments include melatonin (it has anti-gonadotropic activity, although results may take 3-4 months and may not affect adrenal sex steroid hormone synthesis), flaxseed oil with lignins (it has anti-estrogen activity and lowers cortisol enzymes), and ketoconazole (decreases androgen and cortisol production). Surgical options include hypophysectomy (however, anticipated side-effects include hypothyroidism, hypocortisolism, and central diabetes insipidus and the procedure is difficult and with a high morbidity/mortality) and adrenalectomy (although, sometimes medical management is employed to control abnormal hormone levels prior to surgery, or to treat a patient where surgery is not an option due to financial reasons, anesthetic or surgical risks, etc). Radiation therapy is the typical treatment for pituitary macroadenoma, but usually does not resolve the abnormal hormone secretion associated with pituitary dependent HAC

References:

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