Adrenal Dependent Hyperadrenocorticism

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Introduction

Canine hyperadrenocorticism is an endocrine disorder that results from excess production of cortisol by the adrenal glands. Approximately 80-85% of all cases are classified as pituitary dependent hyperadrenocorticism.[1,2] In these cases, excess production of adrenocorticotropic hormone (ACTH) by the pituitary gland causes the adrenal glands to produce abnormally high levels of cortisol

The other 15-20% of hyperadrenocorticism cases are classified as adrenal dependent hyperadrenocorticism.[1,2] In these cases, a mass in the adrenal cortex produces excess levels of cortisol. The purpose of this report is to discuss the patient presentation, diagnosis, pathophysiology of the disease, treatment, and case outcome of a patient diagnosed with adrenal dependent hyperadrenocorticism.

History and Presentation:

Poodles, terriers, labs, and German shepherd dogs are breeds commonly diagnosed with adrenal dependent hyperadrenocorticism.[2-4] Females are more likely to develop this form of hyperadrenocorticism, as well as dogs greater than 20 kilograms.[3] This disease occurs more frequently in older dogs ranging from nine to eleven years in age on average.[4] Common clinical signs include: polyuria/polydipsia, polyphagia, pendulous abdomen, alopecia, skin lesions, hepatomegaly, lethargy, and obesity.

Bill, the patient in this case report, is a 5 year old neutered male Scottish terrier that presented to MSU-CVM Small Animal Internal Medicine department on 10/19/16 for evaluation of hyperadrenocorticism diagnosed by his referring veterinarian. The owner noted that Bill had been eating, drinking, and urinating excessively for about 4 weeks. The owner also noted that Bill had gained moderate amount of weight over the

four week period. The referring veterinarian diagnosed Bill with hyperadrenocorticism via a urine cortisol/creatinine ratio and a low dose dexamethasone test about two months prior to his visit at MSU-CVM.

Diagnostic Considerations

Serum chemistries are useful identifying electrolyte, enzymatic, and protein abnormalities seen in endocrine disorders. Increased serum level ALP is one of the most common clinical abnormalities seen in patients with hyperadrenocorticism.[1,2] Increased serum ALT may also be seen, but these changes are generally mild.[1,2] Increases in serum cholesterol and triglyceride, along with decreases in blood urea nitrate may also be noted.[1,2]

Urinalysis may be used to help identify and distinguish different types of endocrine disorders. Patients with hyperadrenocorticism are often polyuric and polydipsic and thus their urine is dilute with a specific gravity generally less than 1.020.[2] Urine culture in patients with hyperadrenocorticism is often recommended, as patients with excessive levels of cortisol may have some degree of immune suppression. A retrospective study found that 21 of 46 dogs with hyperadrenocorticism had a concurrent urinary tract infection.[15]

A urine cortisol to creatinine ratio, ACTH stimulation test, or a low dose dexamethasone suppression test should be used in patients with suspected hyperadrenocorticism. These tests are used to screen for hyperadrenocorticism and though the tests are not 100% sensitive or specific they are generally useful in correctly identifying patients with hyperadrenocorticism.[1, 2] The urine cortisol to creatinine ratio test has a high sensitivity 100%[16] but a variable specificity (22-78%)[16,17]. Due to the low

cost and high sensitivity, this test is often one of the first tests used to screen for hyperadrenocorticism. The low dose dexamethasone test has a sensitivity of 85-100% and a specificity ranging from 44-77%. [18,19] While this test can provide concrete evidence of hyperadrenocorticism, the low specificity has the potential to produce false positives, and thus the test should not be the only method to diagnose hyperadrenocorticism. The ACTH stimulation test has a sensitivity ranging from 57%-95% and a specificity ranging from 59-93%[20,21]. This test has a high potential to produce false negatives and thus a low dose dexamethasone test is generally preferred over an ACTH stimulation test for screening for hyperadrenocorticism.

Once a diagnosis of hyperadrenocorticism is established, adrenal dependent hyperadrenocorticism must be distinguished from pituitary hyperadrenocorticism. Low dose dexamethasone suppression, high dose dexamethasone suppression, and ACTH concentration are commonly used to differentiate pituitary dependent hyperadrenocorticism and adrenal dependent hyperadrenocorticism. In a case study comparing high dose and low dose dexamethasone tests, 75% of dogs with pituitary dependent hyperadrenocorticism experienced cortisol suppression after administration of the high or low dose dexamethasone test.[22] No cortisol suppression was seen in the patients with adrenal dependent hyperadrenocorticism.[22] In a separate study no cortisol suppression was noted in 41 patients with adrenal dependent hyperadrenocorticism that received low or high doses of dexamethasone.[9] Based on the results of the two studies, cortisol suppression can be used to support diagnose pituitary dependent hyperadrenocorticism. However, if cortisol suppression is not observed, further

diagnostic tests are needed to distinguish pituitary and adrenal dependent hyperadrenocorticism.

Measurement of ACTH, a hormone produced by the pituitary gland, concentrations is the most reliable methods to differentiate the pituitary and adrenal hyperadrenocorticism.[2] Concentrations of ACTH are not elevated in patients with adrenal hyperadrenocorticism and thus an increase of ACTH is diagnostic of pituitary dependent hyperadrenocorticism.[1, 2] However, the accuracy of this test is dependent on the ability of the assay to detect levels of ACTH hormone. Different assays have different analytical sensitivities and thus have varying degrees of detecting smaller increases of ACTH.[22] High cost and extensive sample handling guidelines limit the use of the diagnostic test.

Diagnostic imaging can also provide evidence to distinguish between pituitary and adrenal dependent hyperadrenocorticism. Radiography often shows non-specific signs of disease such as hepatomegaly, bronchial lung patterns, enlargement of the bladder, and calcinosis cutis. However, adrenal adenomas and carcinomas may calcify and this change may be observed on radiographs.[23]

Ultrasonographic imaging is useful in determining adrenal symmetry, width, thickness, diameter, and may be used to visualize neoplastic invasion of vascular or surrounding soft tissue. Symmetrical adrenal glands are generally seen in dogs with pituitary dependent hyperadrenocorticism. [24,25] Significant asymmetry, contralateral adrenal atrophy, invasion into surrounding soft tissue or vasculature are seen in patients with functional adrenocortical tumors.[24, 25] If vascular involvement is suspected it is recommended to follow up abdominal ultrasound with a CT scan, as this diagnostic modality is more sensitive at detecting vascular involvement.[26]

Diagnosis

During Bill's first visit at MSU-CVM, a CBC, serum chemistry, urinalysis, and urine culture were performed. The CBC was within normal limits. On serum chemistry, the liver enzymes, alanine transaminase and aspartate transaminase were significantly elevated (311 U/L, reference range- 10-90 U/L and 1577 U/L, reference range 11-140, respectively). The specific gravity of his urine was determined to be 1.004, indicating that the urine was dilute. The urine culture was negative for bacterial growth. Elevated liver enzymes are supportive of hyperadrenocorticism, and the dilute urine was likely secondary to polyuria and polydipsia. An endogenous ACTH test was also submitted and the levels of ACTH (20 pg/ml normal range 10-80 pg/ml) were found to be within normal

Abdominal radiographs (2 view Ventral-Dorsal and Right Lateral) and an abdominal ultrasound were also obtained. Radiographs revealed hepatomegaly with moderate rounding of the caudal margin. A circular shaped mineral opacity was observed superimposed over the left kidney. Abdominal ultrasound revealed enlargement and thickening (2.4 cm) of the left adrenal gland. The right adrenal gland was decreased in thickness (0.51 cm).

The clinical signs, serum chemistry, urinalysis, endocrine tests, and initial diagnostic imaging were strongly indicative of adrenal dependent hyperadrenocorticism. The owner elected to have the left adrenal gland removed and a CT scan with contrast was performed on 10/21/16. The CT scan revealed a severely enlarged left adrenal gland (3.4 cm x 2.8 cm x 2.8 cm). Mineralization was present and the enlarged gland was causing rightward displacement and caudal compression of the caudal vena cava. However there was no indication that mass on the adrenal gland had invaded the caudal

vena cava. The left adrenal gland was also causing caudal displacement and compression of the left renal vein.

Pathophysiology

The hypothalamus-pituitary-adrenal axis is responsible for normal cortisol production. The hypothalamus regulates pituitary gland function by secreting corticotropin releasing hormone (CRH). Inflammatory mediators such as interleukin 1, tumor necrosis factor alpha, and interleukin 6 stimulate secretion of CRH; dopamine, arginine-vaspressin, and angiotensin II also stimulate secretion of CRH.[2] Stressors, such as hypoxemia, extreme temperatures, pyrogens, pain, and trauma also increase levels of CRH. Increased levels of glucocorticoids, such as cortisol, cause a decrease in CRH production via negative feedback.[1,2]

CRH travels to the anterior pituitary gland via the hypothalamus-hypophyseal portal system, where it stimulates endocrine cells that produce adrenocorticotropic hormone (ACTH). The anterior pituitary gland consists of the pars infundibularis and pars distalis. The pars distalis contains cells known as corticotrophs that are responsible for production of ACTH. The corticotrophs are stimulated to produce ACTH by CRH and are suppressed by increased levels of glucocorticoids. [1,2] The intermediate pituitary lobe is also thought to be responsible for ACTH concentrations in the body.[5,6] Cells known as "B" cells have been shown to stain immunocytochemically positive for ACTH; these cells are thought to produce proopiomelanocortin, the precursor to ACTH. [5, 6]

ACTH travels to the adrenal gland where it stimulates production of cortisol in the adrenal cortex. The adrenal cortex consists of three zones: the outer zona glomerulus, the middle zona fasciculata, and inner zona reticularis. The zona fasciculata is responsible

for production of cortisol. Synthesis of cortisol is mediated by cytochrome P450 enzymes.[2]

In patients with adrenal dependent hyperadrenocorticism, a functional tumor in the adrenal gland produces excessive amounts of cortisol. The tumors are usually unilateral and there is no predilection with regard to side. The high levels of cortisol suppress circulating concentrations of CRH and ACTH. Due to the lack of an active hypothalamic-pituitary-adrenal axis, the contralateral adrenal gland is usually atrophied. A 2005 retrospective study examined 195 adrenocortical masses over a 20-year period. This study found that adrenal adenomas were approximately four (154) times more common than adrenal carcinomas (41).[7] However, analysis of case reports of patients with confirmed functional adrenocortical masses, suggests that carcinoma are more common.[8, 9]

Approximately 50% of patients with carcinoma will have metastatic neoplasia. The liver and lungs are the two most common sites of metastasis. Metastatic neoplasia has also been observed in kidneys, ovaries, thyroid gland, and mesenteric lymph nodes.[10] Tumors greater than two centimeters in diameter or tumors that have invaded into the renal capsule have an increased likelihood of malignancy. [10]

Treatment

Surgical removal of the affected adrenal gland is the current treatment of choice.[11,12] A one to two month pre-surgical course of trilostane is often recommended to alleviate the clinical signs of hyperadrenocorticism and allow the patient to become stable for the surgical procedure. The surgery may be done via a midline approach, flank approach, or laparoscopically. Intraoperative mortality is possible due to the highly

vascular nature of the surgery.[13] Post-operative complications may be life threatening and include: pancreatitis, hemorrhage, electrolyte imbalance, and thromboembolism.[13]

In Bill's case, he was started on trilostane (1.5 mg/kg PO q12) for approximately one week. The owner reported that Bill was lethargic and an ACTH stimulation test was performed at the referring veterinarian. The pre and post ACTH levels were both below normal limits (4.3 μ g/dl and 5.5 μ g/dl respectively). The dosage of trilostane was reduced to (1.0 mg/kg PO q 12) to avoid a potential Addisonian crisis. A second ACTH stimulation test was performed at MSU-CVM on11/8/16 and it was determined that his cortisol levels were low before (<1.0 µg/dl /dl normal 2-6 µg/dl /dl) and after (< 1.0 µg/dl /dl normal 6-18 µg/dl /dl) the stimulation test. At this point, trilostane was discontinued and dexamethasone (0.05 mg/kg PO q 24hrs) was given. After a one week course of dexamethasone, a third ACTH test was performed this time ACTH l levels were 3.1 µg/dl before and 9.3 µg/dl /dl after the stimulation test; due to the results of this stimulation test, it was determined that Bill was stable enough to undergo an adrenalectomy.

On 11/15/16, Bill underwent a left adrenalectomy. He was placed in dorsal recumbency and a 20 cm midline incision was made from the xiphoid process to the pubis. The mass was visualized on the left adrenal gland and was approximately 5 cm in diameter. The mass appeared to have many vascular branches associated with the surrounding renal vasculature. These vessels were meticulous ligated using 3-0 PDS ligatures and hemoclips. After ligation was performed, the mass was removed. Routine closure of the abdomen was performed and recovery from anesthesia was unremarkable.

Postoperatively, Bill was given Enoxaparin (0.8 mg/kg SQ q 6hr) to reduce pulmonary thromboembolism formation. Enoxaparin is a low molecular weight heparin

that reduces the risk of blood clot formation. He was placed on this medication because of vascular manipulation during surgery, and his blood was in a hypercoagulable state due to his hyperadrenocorticism. Two days after his surgery, he began to have difficulty breathing and harsh lung sounds were noted upon auscultation. Thoracic radiographs were obtained and no evidence of fluid overload or pulmonary thromboemboli were observed. As a precautionary measure, Bill was given Clopidogrel (1.0 mg/kg PO q24) for three days. Clopidogrel (1 mg/kg PO q24) is an anticoagulation medication that works by blocking ADP receptors on platelet membranes. ADP is a signaling molecule that promotes platelet aggregation.

Bill also received dexamethasone (0.04 mg/kg PO q12) post operatively for six days and was sent home with Prednisolone (0.2 mg/kg PO q12). Pre-operative abdominal ultrasound revealed that his right adrenal gland was decreased in size. Visualization of the right adrenal during surgery confirmed that the gland was significantly smaller than normal. Atrophy of the adrenal is likely secondary to suppression of the hypothalamic-pituitary-adrenal axis due to excessive cortisol production by the contralateral adrenal gland. Exogenous glucocorticoids were administered to provide adequate levels of cortisol and thus prevent an Addisonian crisis until the normal adrenal gland could recover.

Outcome/Prognosis

The adrenal mass was submitted for histopathology at MSU-CVM. Histopathology determined that the adrenal mass was an adrenocortical adenoma. The Anatomical Pathologist deemed that surgical margins were complete. Median survival

time of patients with adrenocortical adenomas has been determined to be approximately 687.5 days[14]

Bill was discharged on 11/22/16. His referring veterinarian performed a serum chemistry on 12/1/16. His ALT was slightly elevated at 353 U/L (reference range 10-118 U/L). His ALP was not measured and all other chemistry values were within normal limits. There was no concern of elevated ALT at this time due to Bill being on a two-week course of Prednisolone.

On 12/22/16 his referring veterinarian performed an ACTH stimulation test. His pre-stimulation cortisol was 1.4 μ g/dl (reference range states that less than 2 μ g/dl is indicative of Addison's Disease). His post-stimulation test cortisol was 3.9 μ g/dl (reference range states that normal is 6-18 μ g/dl and 2-6 μ g/dl is inconclusive for Addison's Disease).

On 1/31/17, a CBC and serum chemistry were performed by the referring veterinarian. All values on his CBC were within normal limits. Bill's ALT and ALP were elevated (346 U/L reference: 18-118; 376 U/L reference range: 5-160 U/L). A urinalysis was also performed at this time and the specific gravity of this urine was low (1.004).

On 2/17/17, Bill's referring veterinarian performed a low dose dexamethasone stimulation test. The serum value of cortisol before the test was administered was 3.2 μ g/dl, and the 8-hour serum value was less than 1.0 μ g/dl. The reference range of this test states that patients with greater than 1.4 μ g/dl on the 8 hour post stimulation sample have hyperadrenocorticism. Since Bill's value was less than 1.4 μ g/dl at the 8 hour mark, it was determined that his hyperadrenocorticism had resolved. A urinalysis was performed during this visit and his urine was still dilute (specific gravity of 1.017). At

this time, the owner was told that the cause of Bill's PU/PD was unknown at this time and that further tests would have to be performed to reach a diagnosis. Leptospirosis titers, urine culture, and further diagnostic imaging were recommended at this time. As of 5/13/17, no further diagnostics have been performed.

Conclusion

Adrenal masses producing excessive levels of cortisol are an uncommon cause of canine hyperadrenocorticism. Surgical excision is the treatment of choice and if clean margins are obtained, the procedure is considered curative. In Bill's case, histopathology of his mass revealed an adenoma and complete surgical margins were obtained. On 2/17/17, Bill's hyperadrenocorticism was considered to be resolved. Further diagnostic tests must be performed to determine the current cause of his polyuria and polydipsia.

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