“Atypical Hypoadrenocorticism” in the Canine Patient:

A Case Report

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Introduction

Hypoadrenocorticism, commonly referred to as Addison's disease, is a relatively uncommon disease seen in dogs, with a prevalence between 0.06% and 0.28%. However, the prevalence of Addison's disease is increased in certain breeds like the Poodle, Portuguese Water dog, and Nova Scotia Duck Tolling Retriever due to a heritable autosomal recessive trait.[5] Hypoadrenocorticism results from the failure of the adrenal glands to produce an appropriate amount of glucocorticoids, mineralocorticoids, or both. Up to 32% of dogs diagnosed with hypoadrenocorticism only have clinical signs of glucocorticoid deficiency with normal sodium: potassium ratios at the time of diagnosis.[8] Addison's was not reported in dogs until 1953, and numerous accounts were not recorded in the veterinary literature until the 1980's. Knowledge on the pathogenesis, diagnosis, and treatment of canine Addison's disease has expanded greatly since this time.[5] However, dogs with clinical signs of glucocorticoid deficiency only, or atypical Addison's, are suspected to be underdiagnosed.[4]

History and Presentation

Rudy is a 6 year old male neutered lab mix who presented to Mississippi State University College of Veterinary Medicine (MSU-CVM) Internal Medicine Department on June 28, 2017 for a 5 week history of chronic pneumonia. On May 21st, Rudy's owner noticed he had an increased respiratory rate with severe abdominal effort. Immediately, he was taken to his regular veterinarian and diagnosed with pneumonia based on his physical exam, thoracic radiographs, and bloodwork. Rudy had increased lung sounds in his caudal lungs, and his bloodwork revealed a marked leukocytosis, moderate neutrophilia, and marked eosinophilia. At this time, Rudy was

started on amoxicillin/clavulanic acid and enrofloxacin and instructed to return for a recheck five days later, on the 26th. When he returned for his recheck, Rudy's clinical signs remained unchanged, and his bloodwork was only slightly improved. He was then given two more weeks of antibiotics. He returned to his regular veterinarian on June 15th with still no major improvement and appeared to have a decreased appetite as well. His CBC remained unchanged since his last visit, and a chemistry panel revealed a moderate hypoalbuminemia and mild hyperglobulinemia. During this visit, Rudy had an occult 4Dx heartworm test performed, which was negative. At this time, the antibiotics were continued, and Rudy was started on three days of fenbendazole for possible lungworms. Rudy also has a one year history of atopy that has been controlled on oclacitinib (Apoquel). Oclacitininib was discontinued at this time due to its immunosuppressive effects and his concurrent lung disease. Rudy returned to his regular veterinarian on June 22nd (almost one month after initial presentation), and his bloodwork revealed a moderate leukocytosis, moderate neutrophilia, marked eosinophilia, and now a mild normocytic normochromic anemia. At this time, a referral to MSU-CVM's Internal Medicine department was discussed.

On presentation to MSU-CVM on June 28th, Rudy was bright, alert, and responsive with a body condition score of 6/9. Physical exam revealed a normal temperature of 102.2 F, heart rate of 108 bpm, and elevated respiratory rate of 52/min. On thoracic auscultation, there were increased lung sounds bilaterally in the dorsal region of the lungs, but there were no crackles or wheezes auscultated. Rudy also had dry, flaky skin noted along his dorsum. The rest of his physical exam was unremarkable.

Before pursuing further diagnostics, we discussed with Rudy's owners our knowledge of his case that we acquired from his records, but we would like to know some more about his

history. After further discussion, we discovered that Rudy had periods of inappetance, lethargy, and vomiting since his respiratory signs developed. Within the past week, Rudy had 3 episodes of diarrhea with the final episode containing black, runny feces. His owner's report his resting breathing rate ranged anywhere from 50-80 breaths per minute. Rudy also had a long history of nondiscretionary eating. He is allowed free roam to the 7 acres of land he lives on. He was rescued around a year of age and concurrently diagnosed with Demodex and later found to have multiple metal ballistics in his subcutaneous tissues. Rudy also has a history of atopic dermatitis that has been treated with a combination of hydroxyzine and oclacitinib . He currently receives Afoxolaner and Ivermectin/Pyrantel for flea, tick, heartworm, and intestinal parasite prevention.

Due to Rudy's long history of unimproved respiratory rate and effort, thoracic radiographs were obtained. These revealed a moderate to severe unstructured interstitial pulmonary pattern, which was worsened in the caudodorsal lung fields. The unstructrured interstitial pattern coalesced into an alveolar pulmonary pattern. There was also a pleural fissure line noted between the right middle, right caudal, and caudal sub-segment of the left cranial, and left caudal lung lobes. There was an incidental finding of multiple 2.5 mm in diameter metal ballistic balls in the left thoracic body wall. Due to the chronicity of Rudy's disease, his pulmonary patterns suggested the cause to be infectious or neoplastic. The pleural fissure line suggested there could be a small amount of pleural effusion or pleural fibrosis. Since Rudy's thoracic radiographs suggested possible neoplastic metastasis, abdominal radiographs and an abdominal ultrasound were the next diagnostic tests pursued.

Abdominal radiographs were obtained, but these were quite unremarkable, showing only more metallic fragments in the subcutaneous tissues. Next, an abdominal ultrasound was obtained. However, this test also appeared to be slightly unexciting, with only mild thickening of

the small intestines noted at first. The thickened small intestine was suggestive of possible enteritis and inflammatory bowel disease. There was also some slight gallbladder sludge and bilateral nephrocalcinosis, but none of these findings were getting us closer to Rudy's underlying diagnosis. But there appeared to be some difficulty locating the adrenal glands, bilaterally. Since Rudy's presenting complaint was tachypnea, the difficulty in finding the adrenal glands was not emphasized initially. Eventually, however, Rudy's clinical signs of waxing and waning with inappetance, lethargy, and vomiting would suggest the diagnosis of hypoadrenocorticism.

Since Rudy's bloodwork was not submitted to the lab until the end of the day, and we didn't feel that the results would change our plan, we waited until the next day to get our results. Therefore, Rudy's owners elected to take him home and return for a bronchoscopy the following day. However, when we received our bloodwork results these plans changed. The CBC revealed he had a mild leukocytosis of 24.8 K/ul (7.0-22.0), mild neutrophilia of 18,104 /ul (1500-14200), and marked eosinophilia of 10,416 /ul (120-1300). The chemistry revealed a hyponatremia of 138.4 mmol/L (143-153), hypoalbuminemia of 1.8 g/dl (2.5-3.9), hyperglobulinemia of 6.6 g/dl (2.1-4.3), and hypocholesterolemia of 72 mg/dl (140-360). Rudy's urinalysis was unremarkable. At this point, the ultrasound findings and bloodwork results were making us suspicious of Addison's disease.

A baseline cortisol test was performed to rule in the likelihood of Addison's. The results showed a baseline cortisol of < 1.0 ug/dL, suggesting Addison's. In order to confirm our diagnosis, an ACTH stimulation test had to be performed. The test was performed Thursday evening, but results were not available until Friday morning. Rudy was given 0.07 mg/kg of dexamethasone Thursday night, due to the high index of suspicion and concern that the stress of the diagnostic work-up would precipitate an Addisonian crisis. Rudy's post cortisol sample was

also < 1.0 ug/dL, confirming our diagnosis of Addison's disease. On Thursday, after receiving the cortisol sample, we rechecked Rudy's electrolytes. At this time, his sodium levels were still decreased at 141 mmol/L (143-153) and his potassium was within normal reference range at 4.72 mmol/L (3.7 – 5.90). After being hospitalized for 24 hours (with no fluid therapy), Rudy's electrolytes were rechecked and within reference range. Therefore, he was diagnosed with atypical Addison's disease. No bronchoscopy was performed at this time since we wanted to have his Addison's disease under control before being anesthetized. A Baerman test was performed on feces brought in by Rudy's owner, and the results were suspicious of a lungworm infection. However, a repeat Baerman test was performed on a fresh fecal sample, which was negative. Rudy was still sent home with a two-week course of fenbendazole to cover any possible lungworms that were not detected. A urine sample was collected to be submitted for blastomycosis and histoplasmosis antigen screening. Both of these tests came back negative. Rudy was started on prednisone at .5 mg/kg and tapered down to .2 mg/kg over 6 days. At the time of discharge, Rudy had an increased appetite and better attitude. He was to have recheck bloodwork performed in a week and recheck thoracic radiographs in two weeks.

Pathophysiology

The adrenal gland is made up of two parts: the medulla and the cortex. The medulla is responsible for secreting catecholamines, while the cortex secretes glucocorticoids, mineralocorticoids, and androgens. The major secretory products of the adrenal glands in dogs and cats are secreted by the cortex, and these consist of cortisol, aldosterone, and two androgens, dehydroepiandrosterone and androstenedione. The adrenal cortex is divided into three different layers: the zona glomerulosa, zona fasciculata, and the zona reticularis. The outermost layer, the

zona glomerulosa, is responsible for aldosterone secretion, while the zona fasciculata and zona reticularis are responsible for synthesizing androgens and cortisol.[5,2]

Glucocorticoids, most importantly cortisol, are secreted by the zona fasciculata and zona reticularis of the adrenal cortex. Glucocorticoids have many effects throughout the body, and they are vital for normal homeostasis. They are responsible for hepatic gluconeogenesis/glycogenesis, and they enhance protein and fat catabolism. Glucocorticoids also are important in maintaining vascular reactivity to catecholamines like epinephrine and norepinephrine. They also play a role in maintaining normal blood pressure, lessening the effects of stress, and for conserving the normal gastrointestinal mucosa and function. Therefore, deficiency in glucocorticoids can lead to life-threatening situations that include hypotension, hypoglycemia, anorexia, vomiting, diarrhea, weight loss, inability to maintain vascular tone, and endothelial strength. Also, glucocorticoid deficiency can lead to hyponatremia as well, even though this is usually attributed to mineralocorticoid deficiency. The reason behind a low sodium comes from a secondary stimulation of vasopressin secretion. Vasopressin secretion occurs in times of hypovolemia and lack of negative feedback of cortisol.[5,2]

Sometimes, atypical hypoadrenocorticism can be an early clinical manifestation of “typical” hypoadrenocorticism. The main mineralocorticoid, aldosterone, is regulated by the renin-angiotensin axis, the plasma potassium concentration, and vaguely by the plasma sodium and ACTH concentrations. Mineralocorticoids lead to an increased absorption of sodium (and water), and secretion of potassium from the body through the kidney, sweat glands, salivary glands, and intestinal cells. Hypoaldosteronism leads to a reduced extracellular fluid volume, which eventually progresses to the development of hypovolemia, hypotension, reduced cardiac output, and decreased glomerular filtration rate. Hyperkalemia is a result of decreased renal

perfusion, secondary to hypoaldosteronism. The most common clinical signs displayed due to hyperkalemia are cardiac in origin. High potassium leads to decreased myocardial excitability and slowed conduction. If the plasma potassium continues to rise above 10 mEq/L, ventricular fibrillation or cardiac standstill may occur.[5] One would assume that atypical hypoadrenocorticism usually has no effect on mineralocorticoid production, since the electrolytes are not affected. However, studies have proven that normal electrolytes does not necessarily reflect a normal functioning glomerulosa. Atypical hypoadrenocorticism can manifest in three different ways, which includes sparing of the glomerulosa, aldosterone deficiency, with compensation, and secondarily from glucocorticoid administration.[1]

Over 95% of canine hypoadrenocorticism cases will be due to primary hypoadrenocorticism (HA) from bilateral adrenal cortex destruction. However, secondary hypoadrenocorticism can occur in the canine patient.[5] Most cases of primary hypoadrenocorticism are idiopathic, likely due to immune-mediated damage to over 90% of the adrenal cortex. Primary HA can also develop in dogs being treated for hyperadrenocorticism. Secondary HA is due to decreased secretion of ACTH by the pituitary gland. One potential cause is a mass causing pituitary dysfunction. However, the most common cause of secondary hypoadrenocorticism is iatrogenic. Decreased ACTH production develops secondary to long term exogenous glucocorticoid administration. Due to the exogenous glucocorticoid administration, the adrenal glands become atrophied and cannot respond to a release in ACTH adequately.[4]

Diagnostic Approach/Considerations

Dogs with HA can present in a variety of ways, depending on the “stage” of disease.

Usually, dogs without electrolyte abnormalities are typically older before presentation. There can be unusual histories and clinical signs associated with the diagnosis of hypoadrenocorticism.[7] However, Addison's disease also causes very vague, nonspecific clinical signs that can mimic other diseases. The majority of patients present with a history of lethargy, decreased appetite, vomiting, diarrhea, weight loss, and waxing and waning of these signs. Some dogs may also have a history of regurgitation or radiographic evidence of megaesophagus. Dogs that present in crisis, will present with classic signs of hypovolemic shock, which could include weak pulse, pale mucous membranes, prolonged capillary refill time, and sometimes hypothermia. Melena is also a common sign seen in dogs experiencing an Addisonian crisis, due to the disruption in the gastrointestinal mucosa. Atypical Addisonians rarely present with acute signs, since they do not have the typical electrolyte abnormalities. However, hypotension from decreased vascular tone is possible when there is a decreased amount of circulating cortisol. Atypical Addison's can also result in acute collapse from hypoglycemia and hemorrhagic shock, secondary to gastrointestinal hemorrhage.[4]

Bloodwork often contains abnormalities that will make you suspicious of hypoadrenocorticism. The hallmark sign on a serum biochemistry is a hyperkalemia and hyponatremia. However, these electrolyte disturbances are not present in a patient with atypical Addison's.[4] This small subset of patients makes up about 5-10% of dogs with primary hypoadrenocorticism.[7] A mild non-regenerative anemia is more commonly seen in glucocorticoid deficient hypoadrenocorticism from gastrointestinal hemorrhage or chronic disease. Also, a complete blood count will often be lacking a stress leukogram due to the lack in cortisol. Dogs may have hypocholesterolemia present on their serum biochemistry. This is thought to be due to decreased gastrointestinal lipid absorption and chronicity of disease.[6]

Once hypoadrenocorticism becomes a suspected diagnosis, a baseline cortisol concentration is used to exclude the diagnosis. Although almost all dogs with HA have a basal cortisol level of less than 2 μg/dL, some dogs with non-adrenal illness have low baseline cortisol concentrations, and a follow up adrenocorticotrophic hormone (ACTH) stimulation test should be performed for definitive diagnosis. However, a cortisol level greater than 2 μg/dL is helpful in ruling out hypoadrenocorticism.[5]

In order to definitively diagnose hypoadrenocorticism, an ACTH stimulation test must be performed. This test is performed by measuring two serum cortisol samples before and after the administration of synthetic ACTH, commonly known as cosyntropin or tetracosactrin. Administration of 5 μg/kg of cosyntropin has been proven to differentiate dogs with non-adrenal illness from dogs with hypoadrenocorticism, and this dose is preferred due to the cost of synthetic ACTH.[4] However, up to a maximum of 250 μg/dog can be given intravenously (IV). Intramuscular administration is not recommended in dogs with suspected HA, as its absorption from under-perfused muscles has not been examined. The test is performed by collecting a baseline cortisol sample, and then immediately following with a dose of cosyntropin IV. A one hour post cortisol sample should then be collected. A post sample of less than 2.0 μg/dL is supportive of hypoadrenocorticism, while a sample greater than 2.0 μg/dL rules out the disease. The low cortisol level shows there is a lack of response to the ACTH from the adrenal cortex. It is important to remember that a low post-ACTH cortisol level will not differentiate primary from secondary hypoadrenocorticism, but a thorough history should aid in differentiating these two, unless there is an underlying pituitary lesion.[4] Rudy's basal cortisol level was less than 1 μg/dL, which prompted us to perform an ACTH stimulation test. His ACTH post cortisol sample was also less than 1 μg/dL, confirming our diagnosis of hypoadrenocorticism.

There are many times when a patient may present in crisis, and glucocorticoids must be administered prior to definitive diagnosis. Many synthetic glucocorticoids will falsely elevate your ACTH stimulation results. Two common synthetic glucocorticoids that will cross react are prednisone and methylprednisolone. Therefore, these glucocorticoids should be avoided and alternative steroids like dexamethasone or triamcinolone should be given.[4] A single dose of dexamethasone will still suppress post ACTH cortisol concentrations some. However, studies suggest that it is unlikely that a single dose will abolish the response to ACTH.[5]

Two other tests that will supply us with further information about a patients atypical Addison's are endogenous ACTH levels and pre- and post- ACTH stimulation aldosterone levels. Endogenous ACTH is used to differentiate between primary and secondary Addison's. High levels indicated that the dog has primary hypoadrenocorticism from a lack of negative feedback on the pituitary. Low levels are more consistent with secondary disease.[4] Rudy's endogenous ACTH was elevated at 246 pg/ml (10-80), which was supportive of primary hypoadrenocorticism. We also tested Rudy's aldosterone levels before and after his synthetic ACTH administration. Rudy's post- ACTH aldosterone levels were increased at 112 pmol/L (197-2103) from his pre- sample of 43 pmol/L (14-947). However, the post-ACTH aldosterone level was still below the reference range. Theoretically, it would make sense for dogs with atypical Addison's disease to exhibit an increased aldosterone concentration after ACTH stimulation, and typical Addison's patients will have decreased to minimal response to the stimulation.[4] However, most dogs have been shown to have undetectable ACTH-stimulated aldosterone concentrations, even when their electrolytes were within normal reference range (atypical Addison's). Thus, the pathogenesis of atypical and typical hypoadrenocorticism is probably similar if both have low cortisol and aldosterone levels.[7] Some could argue that all dogs

with aldosterone deficiency would actually benefit from the supplementation of mineralocorticoids, even if they were shown to have normal electrolytes. However, due to the high expense, this is not the common therapeutic choice. Instead, dogs are monitored for electrolyte changes over time to determine if they will eventually require mineralocorticoid supplementation.[1]

Treatment and Management

The main difference with dogs diagnosed with atypical hypoadrenocorticism (versus typical) is they do not require mineralocorticoid supplementation. However, dogs diagnosed with atypical Addison's disease should be monitored frequently for electrolyte derangements because they can develop these later on. Many dogs will not progress for years or ever, but careful monitoring is recommended. They should have their electrolytes monitored every 1-3 months for the first year following diagnosis, and then every 6 months thereafter. It is also imperative to educate these owners of the clinical signs to monitor for.[2]

Owners of atypical Addisonians must understand that treatment is needed for the rest of the dog's life. However, treatment for these dogs can be much more affordable since they do not require mineralocorticoid supplementation. Dogs are typically given 0.5-1 mg/kg/day of prednisone immediately following the diagnosis. Over 3-5 days, these dogs should be tapered to 0.1 to 0.22 mg/kg of prednisone. After 2-3 weeks at this dose, they can be gradually tapered to the lowest dose that will manage their clinical signs. Even though these dogs do not require mineralocorticoid supplementation, they are still at risk for progression to complete adrenal failure.

The glucocorticoid dose should be increased (double to triple the normal dose) during

times of stress for the animal. Stressful situations might include surgery, traveling, large crowds, or trips to the veterinarian. The dosage should be increased in these events or any time the owner feels that the dog is not "acting themselves." In anticipation of a stressful event, the dose should be increased the day or morning prior to the stressful event, and this dose should be continued for a few days after the stressful event has passed. The glucocorticoid dose may also need to be increased if clinical signs begin to increase. In contrast, if no clinical signs are present and the dog is showing adverse effects from the glucocorticoids (PU/PD, panting, polyphagia), the dose should be decreased.[4] Any decreases in prednisone dose should be made following consultation with a veterinarian.

Rudy was given dexamethasone sodium phosphate at 0.07 mg/kg while hospitalized overnight. Once discharged, he was sent home with prednisolone at a dose of 0.5 mg/kg twice a day for three days. His dose was then decreased to once a day for the next three days. Then he was administered a dose at .2 mg/kg daily. Rudy was also sent home with a week of sucralfate and omeprazole for gastrointestinal support.

Case Outcome

Today, Rudy is doing well at home on 0.1 mg/kg once a day supplementation with prednisolone. He has had his electrolytes checked regularly, which have always been within normal reference value. His owners also report that his respiratory clinical signs have resolved at home, and he now has a normal resting breathing rate. However, multiple follow up thoracic radiographs have shown that his unstructured interstitial pattern and alveolar pulmonary pattern is improved but still present. At this time, the owners have declined a further workup for Rudy's underlying lung disease, and they have been encouraged to pursue further diagnostics if his

clinical signs return.

References

1. Baumstark, M., Sieber-Ruckstuhl, N., Müller, C., Wenger, M., Boretti, F., & Reusch, C. (2013). Evaluation of Aldosterone Concentrations in Dogs with Hypoadrenocorticism. Journal of Veterinary Internal Medicine, 28(1), 154-159.
2. Ettinger, Stephen J, Edward C. Feldman, and Etienne Cote. *Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat*. 2017. Print.
3. Lathan, P., Moore, G., Zambon, S., & Scott-Moncrieff, J. (2008). Use of a Low-Dose ACTH Stimulation Test for Diagnosis of Hypoadrenocorticism in Dogs. Journal of Veterinary Internal Medicine, 22(4), 1070-1073
4. Lathan, P. Hypoadrenocorticism in Dogs, in Clinical Endocrinology of Companion Animals (ed J. Rand), Chichester, UK. John Wiley & Sons, Ltd, 2013. 1-21.
5. Scott-Moncrieff, J. Catharine. Hypoadrenocorticism in Canine and Feline Endocrinology. Philadelphia, Pa. U.a.: Elsevier Health Sciences, 2015. 485-517.
6. Thompson, A. L., Scott-Moncrieff, J. C., & Anderson, J. D. (2007). Comparison of classic hypoadrenocorticism with glucocorticoid-deficient hypoadrenocorticism in dogs: 46 cases (1985–2005). Journal of the American Veterinary Medical Association, 230(8), 1190-1194.
7. Van Lanen, Kathleen, and Allison Sande. Canine Hypoadrenocorticism: Pathogenesis, Diagnosis, and Treatment. *Topics in Companion Animal Medicine*. 2014;29(4):88-95.
8. Wakayama, J. A., Furrow, E., Merkel, L. K., & Armstrong, P. J. (n.d). A retrospective study of dogs with atypical hypoadrenocorticism: a diagnostic cut-off or continuum?. Journal Of Small Animal Practice, 58(7), 365-371.