Successful Treatment of Hyperadrenocorticism in a 12-year-old Miniature Dachshund with Si Miao San & Trilostane

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Abstract

A 12-year-old, male-neutered (MN) Miniature Dachshund was treated successfully with a dual combination of trilostane and Si Miao San (SMS). The patient presented with clinical signs consistent with hyperadrenocorticism (HAC). The signs began in October 2009 with polyuria (PU), polydipsia (PD) and slightly elevated serum Alkaline Phosphatase (ALKP) values. A presumptive diagnosis of hepatitis was made. Seven months later, the pet presented for continual worsening of the PU, PD, occasional vomiting, and weight gain. At that time pre and post serum ACTH stimulation cortisol levels were obtained and a diagnosis of HAC was made. The pet was started on Vetoryl (trilostane) therapy. Pre and post serum ACTH stimulation cortisol values following trilostane therapy remained normal. The ALKP values continued to increase after trilostane was started and the pet continued to show worsening of clinical signs of PU, PD and vomiting. An exploratory celiotomy was performed to rule out an obstructive mass or cancer as a cause of the vomiting. No obvious explanation of the vomiting was found and a small adrenal mass was observed. After recovery from surgery, the owner elected to add the herbal medication, SMS. The pet was also switched to a high protein and low carbohydrate diet. After the addition of SMS and the food change, the pet has remained clinically normal. The owner elected to stop SMS, but the clinical signs returned within two weeks. After restarting SMS, the pet has been symptom free of HAC.

Introduction

Hyperadrenocorticism (HAC) occurs when the pituitary gland releases too much adrenocorticotropic hormone (ACTH) that in turn stimulates the adrenal gland to produce excess cortisol, or with an adrenal tumor. As a result, clinical signs such as increased thirst and water consumption, increased urination, weight gain, weak muscles resulting in a pot-bellied appearance and behavioral changes occur (Vetoryl, 2008). Ninety-five percent of cases of canine HAC are a result of pituitary gland over-stimulation of the adrenal glands.

To diagnose the disease, a practitioner evaluates all pertinent information that includes serum chemistry profile, pre and post serum ACTH cortisol stimulation tests, clinical signs and a recent history. When HAC is diagnosed, the only approved drug therapy in the United States is Vetoryl™, or trilostane (Dechra Veterinary Products, 2008). Trilostane is an enzyme blocker that prevents the synthesis of cortisol and does not damage cells like Lysodren™ therapy (Hoskins, 2007). The goal of trilostane therapy is to reduce the cortisol production and eliminate the steroid side-effects

physically and internally by suppressing the adrenocortical production (Vetoryl, 2008).

Other drugs are used to treat HAC, one is ketoconazole. This anti-fungal drug suppresses adrenal steroid synthesis; however, the vomiting, diarrhea, anorexia, thrombocytopenia, hepatic toxic side-effects, and transient beneficial results limit the drug's usefulness in treating HAC. A second common drug is selegiline. This drug inhibits the release of ACTH from the pituitary. Unfortunately, selegiline's success has been less than optimal and is not often used. A third drug is mitotane, or Lysodren™. Mitotane is an adrenal toxic drug that kills the hyperplastic adrenal gland. The hyperplastic adrenal gland is typically a result of an over-active pituitary gland. Because normal tissue is targeted, the potential for severe side effects is problematic. The most severe problem noted with mitotane administration is a permanent hypoadrenocorticism (HOC) state. If this occurs, the animal will need lifelong treatment for HOC. Other mitotane side effects include lethargy, ataxia, weakness, anorexia, vomiting and diarrhea. Because of the problems encountered and the need to monitor closely for side effects, mitotane is cautiously prescribed. Trilostane is the treatment of choice and it has several less severe side effects. The side effects of vomiting, diarrhea and slight lethargy, coupled with a high success rate of HAC treatment and the only approved HAC treatment in the United States, makes this drug the treatment of choice.

Treatment of HAC can be complicated and occasionally unsuccessful in alleviating clinical signs or eliminating blood value abnormalities. Non-traditional treatment using Chinese herbs for HAC, in conjunction with traditional treatment, was successful in this case report. Classification of HAC according to Traditional Chinese Medicine (TCM) is an overabundance of Yang energy arising in Damp Heat (Marsden, CIVT Lecture Notes, 2008, pp.137-138). As a result of the excessive energy, the patient will exhibit heat intolerance, restlessness, increased appetite and increase thirst and urine production. Additionally, Damp Heat is worsened by a diet high in carbohydrates such as a processed kibble (Marsden 2008). One of the main formulas in addressing Damp Heat is Si Miao San (SMS), or Four Marvels Powder. The individual herbal ingredients that make up this formula can be found in the appendix section. Other signs of Damp Heat include skin hot to the touch, greasy coat, lichenification and thickening of the skin, slimy vomitus, snoring, copious exudates, weight gain and loose or mucoid stools (Marsden & Wynn 2003).

History

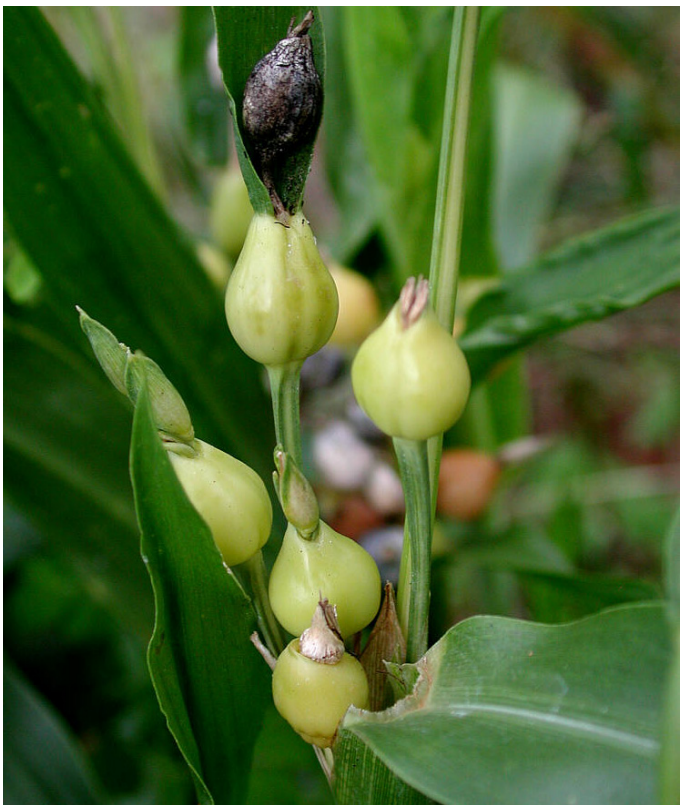
In October 2009, a 12-year-old, MN, Miniature Dachshund was presented for PU and PD. At that time, blood-work was performed to rule out metabolic and endocrine problems. A slight elevation was noted in the serum ALKP value. The patient's blood-work was rechecked in a month and indicated a higher serum ALKP value than the previous month (see appendix A). No treatment was given at that time. In June 2010, the pet presented for worsening of clinical signs of PU and PD and weight gain (see appendix C). An ACTH pre and post serum cortisol level was performed and indicated HAC (see appendix B) due to an elevated response. Once daily trilostane was started and the ACTH stimulation test was re-evaluated two weeks from the start date.

All subsequent pre and post-ACTH serum stimulation cortisol levels have remained normal after beginning the trilostane medication in June 2010 (See appendix B). Despite a normal ACTH stimulation response, the pet continued to have clinical signs consistent with uncontrolled HAC.

In August 2010, the pet presented for a bloated, pot-bellied abdomen consistent with HAC and no resolution of PU and PD. Repeated blood work revealed an increase in serum ALKP (See appendix A). A week later in September 2010, an ACTH stimulation test was performed and was normal. One month later in October 2010, the patient presented for worsening of PU and PD, abdominal bloating and vomiting. Serum ALKP values were higher than the previous values and an abdominal radiograph indicated a possible mid-abdominal mass present, or falciform fat enlargement. An abdominal exploratory was scheduled for the next day. During surgery, a small adrenal mass was observed but no abdominal mass was present to explain the vomiting. A biopsy of the liver revealed vacuolar hepatopathy consistent with hydropic degeneration seen with HAC. A biopsy of the adrenal tumor was not performed to reduce the risk of an anesthetic crisis from excessive cortisol release.

In November 2010, the pet re-presented for vomiting, PU, and PD. Blood work was repeated and revealed a high serum ALKP value and a normal pre and post ACTH serum stimulation cortisol (see appendixes A and B). At this time, the owner was interested in any other treatment options available for the patient. An Eastern examination was performed and revealed oily skin, active acupuncture (AP) points at SP 9 and BL 21, thin skin, a red and damp tongue and a superficial and slippery pulse, all consistent with Damp Heat (DH). The patient was diagnosed with Dampness and Phlegm obstructing the middle burner and an associated accumulation of DH as a result of persistent PU, PD, vomiting, elevated ALKP values, skin abnormalities, active AP points, plus tongue and pulse findings. In November 2010, the patient was prescribed SMS and a high protein and low carbohydrate diet. Liquid SMS from Kan Essential for Animals pet line was started at 0.4cc by mouth, or mixed with food, every 12 hours.

SMS was chosen for the unique properties of each individual herb within the formula. Recent research explains the various benefits noted from SMS. For example, the berberine (Ji et al 2009) within the Phellodendron bark, exhibits hepatoprotective properties to reduce the elevation of liver enzymes (Antelava et al 2011). Coix seeds (pictured below) have



anti-tumor properties found in the fatty acids of the seeds (Cui Tang & Yu 2008). These fatty acids include palmitic, stearic, oleic and linoleic (Moribayashi et al 1994). These particular oils will limit the growth of the adrenal tumor noted on exploratory celiotomy. The third herb, Atractylodes, also possess hepatic protective properties (Chen et al 2010). Additionally, Atractylodesis has gastroprotective benefits (Chang et al 2010). Both hepatic problems and gastrointestinal problems are common side effects noted in a dog with HAC. TCM benefits from the individual herbal ingredients and the actions of each herb can be found in Appendix D.

Two weeks from the start of the herbal medication, the patient became asymptomatic. Two months after starting SMS, the owner discontinued the medications for two weeks. The pet's symptoms of PU and PD returned. Once the owner restarted SMS, the patient returned to normal. Blood work in February 2011 still reveals an elevated serum ALKP that continues to increase despite the pet's normal pre and post ACTH serum cortisol levels, once daily trilostane administration, SMS and a high protein diet. A summary of the physical examination and laboratory abnormal findings can be found in Appendix E.

Discussion

TCM is based on a concept of balanced Qi, or vital energy, which is believed to flow throughout the body. Qi is proposed to regulate a person's spiritual, emotional, mental, and physical balance and to be influenced by the opposing forces of Yin (negative energy) and Yang (positive energy). Disease is proposed to result from the flow of Qi being disrupted and Yin and Yang becoming imbalanced. Pathogenic factors (PFs) that can cause a disruption in the normal energy flow are: Wind, Cold, Heat, Damp, Dryness and Fire. Any of these pathogens, separate or together, can cause an imbalance to the patient. Treating diseases according to TCM is to eliminate the PFs, regardless of the underlying Western disease classification.

If the PFs are eliminated, the patient will return to a normal state of health. TCM does not focus solely on the disease defined by specific pathological changes, but instead concentrates generally on the functional state of the patient (Cai 2011). In this case report, the TCM treatments used to treat HAC in a canine only include herbal medicine and food therapy, in conjunction with once daily oral trilostane administration.

A diagnosis of DH was made based on the history and clinical signs observed in this patient. Dampness includes any overly wet or moist condition in the body. It can come from the environment or it can be due to poor diet or internal organ weakness (Pitchford 2002). Dampness can invade any part of the body and when Dampness affects the intestines and digestion in general, a bloated abdomen and vomiting occur as was seen in this patient (Pitchford 2002). Additionally, Dampness affects water movement throughout the body and can affect urination tendencies that can manifest as PU (Schwartz 1998). Any tumor and excess mucus resulting in vomiting is classified as Dampness (Pitchford 2002).

As this pet has an adrenal tumor and has had several episodes of unexplained

vomiting, this is another indication that the pet can be classified as a Damp patient. DH interferes with the normal Qi and Blood flow, generating Heat as a result of a sort of friction, resulting in abnormal elevated laboratory values, especially ALKP and cholesterol (Marsden & Wynn 2003). Typically, elevations in these values indicate a Middle Jiao Obstruction, as is seen with this pet.

Additional DH signs include an elevated thirst or appetite, but not both, as was evident in this pet (Marsden & Wynn 2003). The tongue and pulse help the practitioner classify a condition according the TCM. With DH signs, the tongue tends to be wet, swollen and red, plus the pulse is slippery (Boudreaux 2007). As a result of the clinical signs present in this pet, the dog can be classified as possessing Damp and Heat causing the clinical signs of PU, PD, vomiting, an adrenal tumor, a bloated abdomen, oily and thin skin, certain active AP points and elevated serum ALKP values, regardless of the Western diagnosis of HAC. In TCM, the pet is classified according to the clinical signs and treated appropriately. This is a reason that one disease classification in Western medicine can have several Eastern treatment options, depending on the classification of the clinical signs present in TCM terms.

The diet can contribute to the Damp signs. Damp contributing foods include refined or highly processed diets as seen in commercial dog kibble (Pitchford 2002). This pet was eating a common commercial over-the-counter dog food, resulting in worsening of Damp clinical signs. Once the owner started to feed a diet higher in protein and lower in carbohydrates, the pet's clinical signs of Dampness began to abate, but not completely. The most notable change was weight loss. The diet can influence the outcome of Dampness in the body. The diet alone was not adequate enough to prevent all clinical signs. A home-cooked or raw diet should prevent sustained elevated insulin levels and cortisol stimulation. Additional treatment was needed to keep the pet asymptomatic.

SMS was prescribed because the herbal formula is used to correct DH signs in patients regardless of the Western diagnosis. The individual herbal ingredients in SMS can be found in Appendix D with a detailed description of each herb and the benefits noted. In summary, Atractylodes dispels Dampness, Phellodendron clears Heat and drains Damp, Coix drains Damp, and Achyranthes relieves hot conditions. This pet benefited from SMS because the formula addressed the main problems the pet was experiencing with HAC.

SMS plus a high protein and low carbohydrate diet was prescribed for this pet. When the pet is on oral trilostane, SMS, and a high protein diet, the pet is asymptomatic. The elevation of the ALKP values and clinical signs consistent with HAC are explained by trilostane's short duration of action of 13 hours or less in some pets. This was demonstrated with the failure of eight of nine dogs in one clinical trial. The pre and post ACTH cortisol stimulation results 12 hours after the once daily administration did not reveal the same normal results as the two hour stimulation test (Bell et al 2006).

This patient was diagnosed with HAC controlled with trilostane medication according to the pre and post ACTH

serum cortisol stimulation tests, but not according to the clinical signs and the continued elevated ALKP values. Once other treatments were added, such as a change in diet and SMS, the clinical signs of PU, PD and vomiting were eliminated. Unfortunately, the ALKP values continue to increase as a result of a proposed failure of the short acting once daily trilostane medication.

Even though the pet is clinically normal, the elevated liver enzyme is concerning and possibly an increase to twice daily, off-label, administration of trilostane will make this patient clinically normal in both observed, subjective clinical signs and objective, diagnostic tests.

Appendix A

Pre-trilostane ALKP Values

	10/29/09	11/5/09
ALKP (N: 23-212)	913	1,000

Post-trilostane ALKP Values

	6/22/10	8/26/10	10/20/10	11/3/10	2/14/11
ALKP (N: 23-212)	1,057	1,838	2,000	1,843	2,310

Appendix B

Serum ACTH Stimulation Tests

	6/9/10	6/24/10	9/8/10	11/19/10
Pre-ACTH Cortisol (N: 6-18)	6.9	2.3	6.8	5.7
Post-ACTH Cortisol (N: 18-22)	34	6.6	11.5	17.3

Appendix C

Weight

	8/26/09	9/22/09	6/9/10	6/24/10	11/19/10
Weight (lbs)	14	12.6	15	13.6	13.4

Appendix D

Si Miao San (Four Marvels Powder) Herbal Content (CIVT 2008)

Herb	Common Name	Action
Huang Bai	Phellodendron Bark	Drain Damp and clears Heat from the Lower Burner
Yi Yi Ren	Coix Seeds	Leaches Dampness, clears Heat and supports the Spleen, Insulin Sensitizing Effects
Cang Zhu	Atractylodes Rhizome	Warms and dries the Spleen and disperses Dampness
Huai Niu Xi	Achyranthes Root	Relaxes the sinews of the low back and moves Blood

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Appendix E

Physical Examination and Laboratory Abnormal Findings

Date	Western Evaluation	Eastern Evaluation
10/09	ALKP 913 (N=23-212)	Middle Jiao Obstruction
	PU	Damp Heat
	PD	Damp Heat
11/09	ALKP 1,000 (N=23-212)	Middle Jiao Obstruction
6/10	Weight Gain	Damp
	PU	Damp Heat
	PD	Damp Heat
	ALKP 1,057 (N=23-212)	Middle Jiao Obstruction
8/10	ALKP 1,838 (N=23-212)	Middle Jiao Obstruction
	PU	Damp Heat
	PD	Damp Heat
	Pot bellied	Damp
10/10	PU	Damp Heat
	PD	Damp Heat
	Vomiting	Damp
	Pot bellied	Damp
	ALKP 2,000 (N=23-212)	Middle Jiao Obstruction
	Adrenal Mass	Damp
11/10	ALKP 1,843 (N=23-212)	Middle Jiao Obstruction
	Tongue: red and damp	Damp Heat
	Pulse: Superficial and slippery	Damp Heat
	Oily skin	Damp
	SP 9 active point	Damp
	BL 21 active point	Damp secondary to inappropriate diet
	Thin skin	Deficiency
2/11	ALKP 2,310 (N=23-212)	Middle Jiao Obstruction

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