Case Reports

Cardiogenic Pulmonary Edema in a Dog Following Initiation of Therapy for Concurrent Hypoadrenocorticism and Hypothyroidism

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Abstract

A 5 yr old intact female cocker spaniel dog weighing 7.8 kg was referred with anorexia, vomiting, and depression. At referral, the dog was diagnosed initially with typical hypoadrenocorticism, and 2 d later, concurrent primary hypothyroidism was detected. Hormonal replacement therapies, including fludrocortisone, prednisolone, and levothyroxine, were initiated, but a few days later the dog became abruptly tachypneic, and thoracic radiographs indicated the development of pulmonary edema. Echocardiography showed that there were abnormalities indicating impaired left ventricular function, although the heart valves were normal. Following treatment with pimobendan and furosemide, the pulmonary edema resolved. The dog had no recurrence of the clinical signs after 10 mo of follow-up, despite being off all cardiac medications; consequently, the cardiac failure was transient or reversible in this dog. The case report describes the stepwise diagnosis and successful treatment of cardiogenic pulmonary edema after initiation of hormonal replacement therapy for concurrent hypoadrenocorticism and hypothyroidism in a dog. (J Am Anim Hosp Assoc 2016; 52:378–384. DOI 10.5326/JAAHA-MS-6225)

Introduction

Polyendocrinopathies have been reported in only single case reports or small case series in veterinary medicine, so there is a lack of information about successful treatments for combined hypoadrenocorticism and hypothyroidism in dogs. Endocrine hormone deficiencies have been associated with cardiac dysfunction and heart failure. Among hormone deficiencies causing cardiac abnormalities in humans, the most consistently reported is hypothyroidism. In dogs, there has been only one report of dilated cardiomyopathy and congestive heart failure caused by hypothyroidism. The link between adrenal insufficiency and heart failure has been described in humans. However, to the best of the authors’ knowledge, it has not been reported previously in dogs. The case reported herein describes the diagnosis and treatment of cardiogenic pulmonary edema after hormonal replacement therapy for concurrent hypoadrenocorticism and hypothyroidism in a cocker spaniel dog.

Case Report

A 5 yr old intact female English cocker spaniel dog weighing 7.8 kg was referred with a 2-wk history of anorexia, vomiting, and depression. Serum biochemical analyses performed by the referring veterinarian 13 d earlier detected moderate hyponatremia (119 mmol/L; reference interval (RI) = 141–152 mmol/L) and elevated blood urea nitrogen (157 mg/dL; RI = 7–25 mg/dL) and creatinine (4.0 mg/dL; RI = 0.5–1.5 mg/dL). The abnormalities improved dramatically within 48 h with fluid therapy, although they recurred after a few days.

At referral (day 0), the dog appeared slightly lethargic. Cardiac auscultation detected an irregular rhythm bradycardia with a heart rate of 60 beats per minute but no heart murmur. The mucous

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membranes were dry and tacky, and a skin tent was visible. The systolic arterial blood pressure (RI = 110–160 mmHg), measured using an indirect Doppler technique, was 60 mm Hg with a prolonged capillary refill time. Due to severe dehydration, fluid therapy consisting of 0.9% sodium chloride at a rate of 40 mL/kg/h for the first 1 h, was promptly initiated to reestablish an effective circulating blood volume and adequate organ perfusion. The initial diagnostic evaluation included a complete blood count, a serum biochemistry profile, urinalysis, electrocardiogram (ECG), thoracic and abdominal radiography, abdominal ultrasonography, and an adrenocorticotropic hormone (ACTH) stimulation test. The complete blood count was unremarkable except for a mild eosinophilia (1529/µL; RI = 100–1300/µL). The abnormal biochemistry profile results included severe hyperkalemia (9.2 mmol/L; RI = 3.6–5.8 mmol/L) with hyponatremia (125 mmol/L; RI = 141–152 mmol/L), hypercalcemia (13.5 mmol; RI = 9–11.3 mmol/L), hyperphosphatemia (14.6 mmol/L; RI = 2.6–6.2 mmol/L), elevated blood urea nitrogen (145.1 mg/dL; RI = 7–25 mg/dL), elevated creatinine (4.2 mg/dL; RI = 0.5–1.5 mg/dL), and hypoglycemia (38 mg/dL; RI = 65–118 mg/dL) (Table 1). The urine specific gravity was 1.016, indicating inadequate concentration in the face of dehydration. The thoracic radiographs revealed a narrow posterior vena cava; this suggested severe dehydration in agreement with the physical examination findings (Figure 1A). In addition, there was an alveolar and interstitial pattern in the left caudal lung field, suggesting pneumonia or non-cardiogenic pulmonary edema of unknown etiology; however, the dog showed no clinical signs of pneumonia. Both adrenal glands were reduced in thickness (left 2.7 mm, right 3.0 mm; RI = 3.2–7.4 mm), which was the only significant finding of the abdominal ultrasound examination.11,12 The ECG detected an irregular rhythm with a ventricular rate of 70–80 beats per minute (Figure 2A). The ACTH stimulation test showed that the cortisol was below the detection limit (<1.00 µg/dL; RI = 0.5–4 µg/dL) at baseline, and the 1-h post-cortisol (<1.00 µg/dL; RI = 8–20 µg/dL) concentration failed to increase after synthetic ACTHa administration (0.25 mg/dog). Based on these findings, the dog was diagnosed with hypoadrenocorticism that led to severe dehydration. The dog was hospitalized in an intensive care unit, and an intravenous injection of dexamethasone phosphateb (0.5 mg/kg) was given. Thereafter, 0.9% sodium chloride plus 5% dextrose was administered intravenously at a rate of 8 ml/kg/h for the next 5 h, after which the rate was maintained at 2.5 ml/kg/h. Fludrocortisone acetatec (0.01 mg/kg) and prednisoloned (0.1 mg/kg) were prescribed twice daily, starting at 24 h after the administration of dexamethasone.

On day 2, the serum chemistry abnormalities were not detected (Table 1), but the dog remained lethargic and anorectic and exhibited a sustained bradycardia with a ventricular rate of 50–60 beats per minute on the ECGe (Figure 2B). The thyroid function was evaluated and the results showed that the serum total thyroxine (TT4) (<0.30 µg/dL; RI = 1.0–4.0 µg/dL) and free thyroxine (<0.3 ng/dL; RI = 0.6–3.7 ng/dL) concentrations were below the detection limits, while there was an elevated level of canine thyroid-stimulating hormone (0.88 ng/ml; RI = 0.05–0.42 ng/ml). Thus, the dog was diagnosed with polyendocrinopathyp with concurrent typical hypoadrenocorticism and primary hypothyroidism. Administration of levotyroxinef (0.01 mg/kg, PO, q 12 h) was added to the prescription. On day 4, the dog was more active
and had a normal appetite, and her heart rate was within the normal reference range (Figure 2C). The following day, the administration of IV fluid was discontinued.

On day 6 of hospitalization, however, the dog became acutely tachypneic. Thoracic radiographs revealed a diffuse increased alveolar and interstitial pattern that was most severe in the hilar region. This was consistent with pulmonary edema (Figure 1B). Echocardiography detected myocardial regurgitation despite normal-appearing mitral valve leaflets. The echocardiographic results were as follows: a normal fractional shortening (FS) (35.6%; RI = 33–46%); increases in the left ventricular internal diameter at end diastole (32.65 mm; RI = 23.8–27.8 mm) and the left ventricular internal diameter at end systole (21.02 mm; RI = 13.7–16.5 mm); decreases in the interventricular septum at end diastole (4.9 mm; RI = 6.8–8.2 mm), interventricular septum at end systole (7.35 mm; RI = 10.2–11.8 mm), left ventricular posterior wall at end diastole (4.08 mm; RI = 5.4–6.6 mm), and left ventricular posterior wall at end systole (7.76 mm; RI = 13.7–16.5 mm). These findings suggested a dysfunctional, dilated left ventricle, as well as an abnormal myocardial wall thickness. In the blood samples collected on day 4, the levels of cardiac biomarkers, including amino terminal probrain natriuretic peptide (>3,000 pmol/L; RI = 0–900 pmol/L) and cardiac troponin I (0.7 ng/mL; RI < 0.2 ng/mL), were much higher than the RIs of normal dogs. Thus, her pulmonary edema was probably related to cardiac dysfunction; therefore, twice-daily oral administration of pimobendan (0.25 mg/kg) and furosemide (2 mg/kg) was initiated promptly. On day 7, the thoracic radiographs detected reduced pulmonary edema, and the dog’s tachypnea was improved. On day 9, she was discharged.

On day 11, the owner reported that the dog remained lethargic and had no appetite, but the thoracic radiographs showed no evidence of pulmonary edema. Mild hyponatremia (134 mmol/L; RI = 141–152 mmol/L) was the only abnormal feature of the serum biochemistry. Administration of furosemide was tapered. On day 16, the TT4 level was determined 4 h after pill administration, and it was found to be within the RI (1.1 μg/dL; RI = 1.0–4.0 μg/dL) but below the therapeutic range. The dose of levothyroxine was increased by 25% (0.0125 mg/kg, PO, q 12 h), the mineralocorticoid replacement therapy was changed from fludrocortisone acetate to deoxycorticosterone pivalate (DOCP) (2.2 mg/kg, IM, q 25 d), and the dosage of prednisolone was increased from 0.1 mg/kg (q 12 h) to 0.5 mg/kg (q 12 h). On day 22, her overall body condition, including physical activity and appetite, was assessed as normal. On day 79, there were no serum chemistry abnormalities, and the echocardiographic evaluation revealed only mild improvements in the left ventricular internal diameter at end diastole (30.42 mm), interventricular septum at end diastole (6.53 mm), and left ventricular posterior wall at end diastole (7.49 mm). However, there was no improvement in the left ventricular internal diameter.
at end systole (23.99 mm), and the FS (21.1%) was decreased despite a return to euthyroidism (TT4, 1.69 l g/dL; RI = 1.0–4.0 l g/dL). The levels of amino terminal probrain natriuretic peptide and cardiac troponin I had returned to normal. The dose of levothyroxine was increased by 25% (0.015 mg/kg, PO, q 12 h).

On day 144, although a subsequent echocardiographic examination failed to reveal a significant improvement, the administration of pimobendan was discontinued with the consent of the owner, because there was no evidence for the recurrence of signs of congestive heart failure.

At 10 mo after presentation, the dog continued to do well clinically, and the serum TT4 concentration was 2.1 µg/dL. The current medications comprised 0.015 mg/kg of levothyroxine twice daily, a single daily physiological dose of 0.3 mg/kg of PDS, and 2.2 mg/kg of DOCP every 25 days.

**Discussion**

In this case, a dog was diagnosed as suffering from a polyendocrinopathy, which comprised hypoadrenocorticism and hypothyroidism, and, after the initiation of hormonal replacement therapy, developed suspected cardiogenic pulmonary edema. Although the exact cause of the pulmonary edema was difficult to determine, several possibilities were considered, such as the effects of the two endocrine diseases (hypoadrenocorticism and hypothyroidism) and the effect of hormonal replacement therapy on cardiac function.

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**FIGURE 2** Electrocardiographs (ECGs) recorded from a cocker spaniel dog with hypoadrenocorticism and hypothyroidism. (A) At initial presentation, the lead II ECG detected an intermittent loss of P wave, a decreased QRS amplitude, and peaking of the T waves with a ventricular rate of 78 beats/min, which were consistent with hyperkalemia, while the serum potassium concentration was 9.2 mmol/L at this time. (B) Lead II ECG recording after correction of hyperkalemia. The ECG detected a junctional rhythm for first, third, and fifth complex with small QRS complexes, followed by peaking of the T waves and a heart rate of 54 beats/min. (C) Lead II ECG recording after the administration of levothyroxine. The ECG detected a heart rate of 120 beats/min.
First of all, we considered the possibility that fludrocortisone administration contributed to volume overload. Fludrocortisone acetate, a synthetic steroid with potent mineralocorticoid action, has been reported to have a number of side effects, including congestive heart failure, hypernatremia, hypokalemia, and hyperglycemia.\textsuperscript{13} In humans, fludrocortisone acetate administration at an optimal dose resulted in congestive heart failure in an infant diagnosed with hypoadrenocorticism who had developed systemic hypertension as a result of the treatment.\textsuperscript{14} In two other cases of fludrocortisone therapy for hypoadrenocorticism, a pediatric patient experienced peripheral edema and cardiac failure, despite the fact that the dose employed was within the doses specified by pediatric endocrinology guidelines and an adult patient experienced pulmonary edema 2 wk after the administration of an optimal dose of fludrocortisone.\textsuperscript{8,9} The authors speculated that renal adaptation to chronic salt and water deprivation may have played a role in the sensitivity of these patients to fludrocortisone replacement therapy.\textsuperscript{8,9} That is, once mineralocorticoid replacement treatment was begun, the previous adaptive mechanism may have resulted in sodium and water retention, leading to congestive heart failure.\textsuperscript{8,9} To the authors’ knowledge, there have been no previous reports of an association between congestive heart failure and fludrocortisone therapy for hypoadrenocorticism in dogs.

In the present case, there was no suggestion of abnormal myocardial function in the dog prior to the presentation. The initial dose of fludrocortisone was consistent with reported recommendations. Hypotension resolved and the dog remained normotensive following therapy with fludrocortisone, glucocorticoid, and IV fluids. However, pulmonary edema unexpectedly developed 6 d after the initiation of fludrocortisone therapy, and echocardiography showed a dysfunctional, dilated left ventricle and a normal FS. It is possible that, in the presence of normal myocardial function, the increase in the circulating volume initially produces a corresponding rise in contractility; however, the increased size of the left ventricle combined with a decreased wall thickness and normal FS in a moderate mitral regurgitation setting indicates a significant reduction in myocardial contractility. Therefore, we assumed that the congestive heart failure was caused by poor left ventricular contractility, and although we could not confirm decisively that fludrocortisone therapy was the cause of congestive heart failure, it could at least have been a contributory factor for the congestive heart failure.

Second, there was the possibility that myocardial dysfunction was caused by glucocorticoid insufficiency. Glucocorticoids have been shown to be important for the maintenance of membrane calcium transport in the cardiac sarcoplasmic reticulum in rats, which may affect myocardial contractility.\textsuperscript{15} It has also been demonstrated that rats may develop impaired myocardial excitation-contraction coupling because of reduced phosphorylase activity following adrenalectomy.\textsuperscript{16} The dog reported here was diagnosed with hypoadrenocorticism immediately at presentation, but presumably also had an unrecognized preceding chronic adrenal insufficiency. The absence of a variety of glucocorticoid effects required for the maintenance of the adrenergic tone in the vascular bed could have contributed to the low systemic vascular resistance. Therefore, afterload at initial presentation may have been depressed and could have masked the poor contractile state. In this respect, there was a possibility that the depressed contractile state of the left ventricle only became obvious after volume resuscitation and the increase in afterload.

Last, the dog had thyroid hormone insufficiency. It has been shown that a rapid return to a euthyroid state can sometimes result in myocardial ischemia.\textsuperscript{5} Furthermore, the higher metabolic rate associated with a return to a euthyroid state can increase myocardial workload and contribute to the likelihood of heart failure.\textsuperscript{17,18} In addition, because thyroid hormone supplementation can increase myocardial oxygen demand, thyroid hormone supplementation in hypothyroid dogs with underlying cardiac disease may cause cardiac decompensation.\textsuperscript{19} Therefore, we speculated that thyroid hormone therapy was decisive for the development of congestive heart failure in our case. The current recommendations for hypothyroid dogs with cardiac disorders include an initial dose of thyroid hormone replacement, which should be 25% to 50% of the usual starting dose, followed by a gradual increase to avoid a sudden change in metabolic demand.\textsuperscript{19} It has also been suggested that the initial dose of levothyroxine should be decreased to 50% of the usual dose in hypothyroid dogs with concurrent hypoadrenocorticism because the increased basal metabolic rate may exacerbate electrolyte disturbance.\textsuperscript{19,20} Although we initially used a dose of levothyroxine that was half the currently recommended guidelines for hypothyroid dogs with concurrent hypoadrenocorticism, the dog nonetheless developed congestive heart failure. Therefore, we advocate the use of a conservative dose of levothyroxine during initial therapy (i.e., 25% of the recommended dose).

Meanwhile, the myocardium is known to be especially sensitive to the effects of thyroid hormone.\textsuperscript{4–6,21} Therefore, decreased concentrations of circulating thyroid hormone are associated with many clinically recognizable effects, including a lower heart rate, a lower inotropic state of the myocardium, and a dilated intraventricular lumen.\textsuperscript{4–6,21} Although it is still controversial whether hypothyroidism truly causes significant clinical cardiac disease, congestive heart failure associated with reduced myocardial contractility has been documented in two hypothyroid dogs and
Compensate for the increased cortisol clearance owing to the or three times their usual glucocorticoid replacement dose to insufficiency and untreated hyperthyroidism should receive two humans, it has been suggested that patients with adrenal function. In our case, the dose of prednisolone was increased from 0.1 mg/kg (q 12 h) to 0.5 mg/kg (q 12h), with the increase in the dose of levothyroxine and the switching from fludrocortisone to DOCP. The increase in the prednisolone dose was because cortisol clearance could be affected by thyroid function. The increased metabolic rate accompanying thyroxine replacement in the hypothyroid patients increases the cortisol requirements. In humans, it has been suggested that patients with adrenal insufficiency and untreated hyperthyroidism should receive two or three times their usual glucocorticoid replacement dose to compensate for the increased cortisol clearance owing to the hyperthyroid state. Moreover, it is recommended that thyroxine replacement in patients with hypothyroidism should start to prevent adrenal crises after the adrenal insufficiency has been excluded or treated. Therefore, in the present case, it was possible that the levothyroxine supplementation to overcome chronic hypothyroid state might have resulted in the increased cortisol clearance. However, there is a lack of evidence on the correlation between the cortisol clearance and thyroxine replacement in dogs.

In conclusion, the pathophysiology of congestive heart failure in this dog might have been multifactorial, although the dog's pulmonary edema appeared to be a consequence of the effect of hormonal replacement therapy on cardiac function. There was a possibility that the dog had underlying heart disease that was subclinical and exacerbated by having two endocrine disorders. It is also possible that the patient developed congestive heart failure secondary to all of our therapies, not just the hormonal therapy, because the dog initially received fairly aggressive fluid therapy. Therefore, in cases of concurrent hypoadrenocorticism and hypothyroidism, initial treatment should be chosen carefully, with proper evaluation of cardiac function, to prevent the development of circulating volume overload. Further study will be necessary to clarify the effect of hormone replacement therapy on cardiac function.

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REFERENCES


