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Case Report

A case of adrenal gland dependent hyperadrenocorticism with mitotane therapy in a Yorkshire terrier dog

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Hyperadrenocorticism, a disorder characterized by excessive production of cortisol by the adrenal cortex, is well-recognized in dogs. A 10-year-old, intact male, Yorkshire terrier dog was evaluated because of corneal ulceration and generalized alopecia. Diagnosis was made based on history taking, clinical signs, physical examination, and results of routine laboratory testing (complete blood count, serum biochemical analysis, and urinalysis). In addition, adrenocorticotropic hormone (ACTH) stimulation test and abdominal ultrasonography were also used to diagnose this case. The patient was diagnosed as adrenal gland neoplasia and medical therapy using the adrenocorticolytic agent, mitotane, was initiated. An ACTH stimulation test was performed after initial therapy. After successful induction was obtained, maintenance therapy with mitotane still continued.

Key words: adrenal gland tumor, dog, hyperadrenocorticism

Hyperadrenocorticism (HAC) is a common multi-systemic endocrine disorder in dogs [2]. Approximately 85% of dogs with HAC results from excessive secretion of adrenocorticotropic hormone (ACTH) from pituitary gland. Adrenocortical neoplasia autonomously secretes an excessive quantity of cortisol independent of endogenous corticotropin control. Characteristics of HAC caused by an adrenal tumor include high baseline serum cortisol concentration that remain high during high dose dexamethasone testing, low or low reference range values (low-normal) for plasma ACTH concentrations, and a solitary, unilateral adrenal mass, as revealed by adrenal imaging studies [5].

Therapy in patient with adrenal gland dependent hyperadrenocorticism (ADH) was mitotane administration and/or surgical intervention. In particular, mitotane is a patent adrenocorticolytic agent, causing necrosis of adrenal cortex (zona fasiculata and reticularis) to decrease cortisol level in serum.

In this case, ADH was differentiated from pituitary-dependent hyperadrenocorticism (PDH) by using a high-dose dexamethasone suppression test (HDDST), endogenous ACTH concentrations, abdominal ultrasound, or a combination of these methods.

The purpose of this case report was to present that mitotane administration was effective and acceptable in dogs with cortisol-secreting adrenocortical tumors and periodical ACTH stimulation test was important to monitor responsiveness to mitotane therapy in Cushing's disease.

Case history

A 10-year-old, intact male, Yorkshire terrier was referred to the Veterinary Medical Teaching Hospital of Konkuk University due to the endocrinological and dermatological problems, such as polyuria, polydipsia and polyphagia. The abnormal physical findings at presentation were corneal ulceration, generalized alopecia (Fig. 1), abdominal enlargement (Fig. 2), patellar luxation, and bilateral cataract.

Blood sample was taken for routine hematological and serum biochemical analysis. The hemogram revealed stress leukogram and thrombocytosis ($665 \times 10^3/\mu l$; reference range, $200\sim500 \times 10^3/\mu l$). Abnormal serum chemical findings were increased alanine aminotransferase (400 U/l: reference range, 13~53 U/l), gamma glutamyl transpeptidase (237 mg/dl; reference range, 1~28 mg/dl), hypertriglyceridemia (653 mg/dl; reference range, 20~155 mg/dl), hypercholesterolemia (360 mg/dl; reference range, 70~303 mg/dl), and typically high alkaline phosphatase (1739 U/l; reference range, 0~142 U/l). Urine sample was obtained by cystocentesis. Results of urinalysis revealed isosthenuria and mild proteinuria. Fungal culture performed to identify dermatophytosis with both dermatophyte test medium (DTM) and Sabouraud dextrose agar (SDA) was negative.

Abdominal radiographic findings revealed hepatomegaly (Fig. 3), gas-filled small intestine, and enlarged prostate. Mineralization and collapse (grade II) of the trachea on

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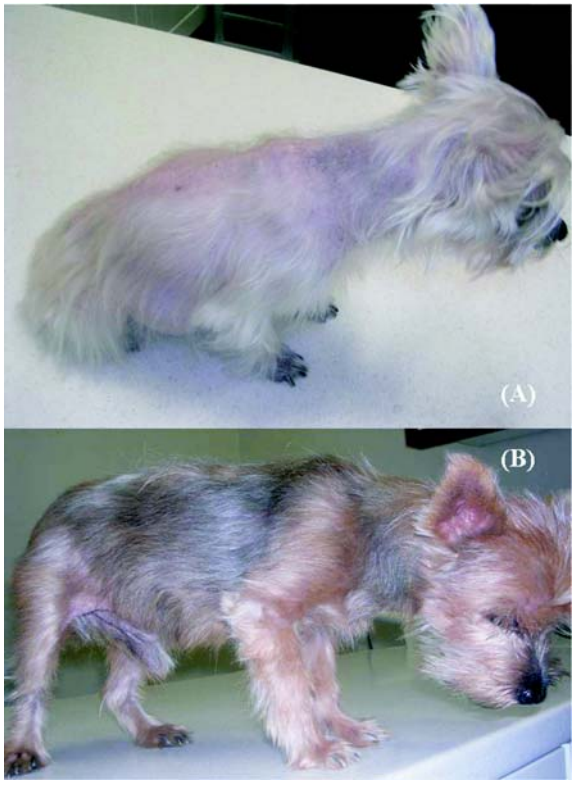

Fig. 1. Generalized alopecia, pigmentation of trunk and neck, and faded hair-coat before administration of mitotane (A). Clinical signs including alopecia and faded hair-coat were alleviated after mitotane therapy (B).

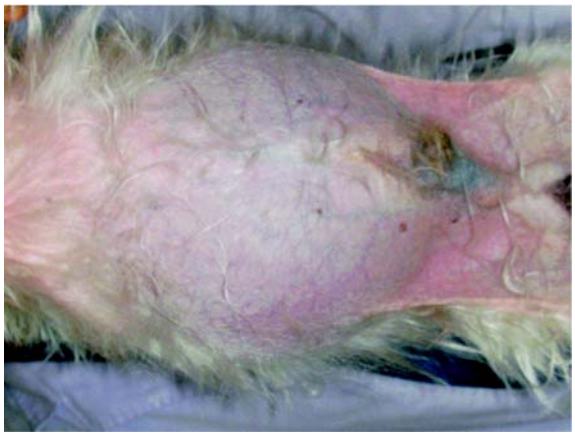

Fig. 2. Pot-belly abdomen in a dog with adrenal-dependent hyperadrenocorticism. Note engorgement of cutaneous blood vessels and thin skin.

thoracic radiography were found (data not shown). Unilateral adrenal gland mass was identified on abdominal ultrasonography (Fig. 4). The ultrasonographic image of this case was mildly mineralized and hyperechoic. However, in this case, areas of necrosis or hemorrhage were not noted. The size of right-side adrenal gland was 1.5 × 1.7 cm in diameter.

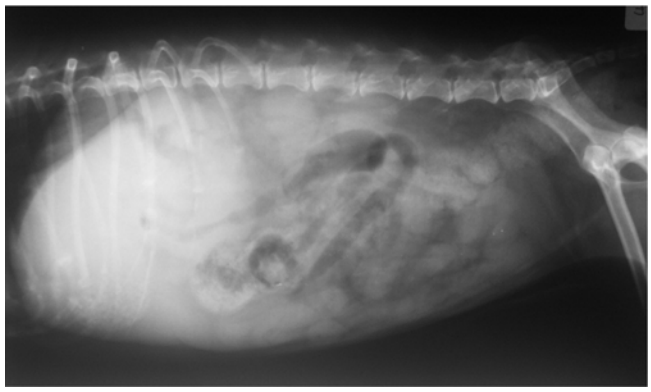

Fig. 3. Lateral radiographic view. Note the distended abdomen and mildly to moderately enlarged liver.

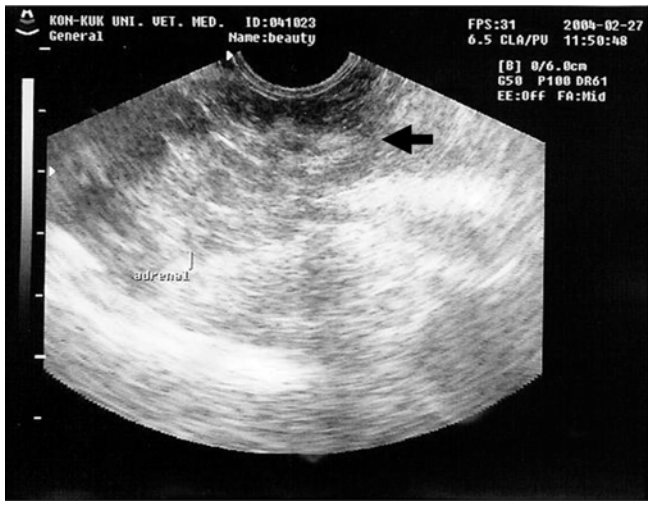

Fig. 4. Longitudinal ultrasonogram of the right-sided adrenal gland mass (arrow). The adrenal gland appears as round mass with mild mineralization and hyper-echogenicity. There was no difference in the adrenal gland size before or after mitotane therapy.

A tentative diagnosis of HAC was based on the history, results of physical examination, and results of routine hematologic and serum biochemical test. Spontaneous HAC was confirmed by distinct increase in serum cortisol concentration in 1 hr after administration of ACTH (Synacthen; 0.25 mg, IM, Novartis Pharma, Swiss). The pre-ACTH cortisol concentration was 3.6 μg/dl (reference range; 0.5~6 μg/dl), and post-ACTH cortisol concentration was 92.8 μg/dl (reference range; 6~17 μg/dl).

ADH was diagnosed on the basis of lack of suppression of serum cortisol concentration at 0, 4, and 8 hrs after administration of a high dosage of dexamethasone (1.0 mg/kg, I.V), together with the finding of low to low normal endogenous plasma ACTH concentration. The pre-HDDST cortisol concentration was 3.2 μg/dl, and cortisol concentration of 4 and 8 hrs after HDDST was 4.8 μg/dl and 5.3 μg/dl, respectively. The endogenous ACTH concentration was

22.9 pg/ml (reference range; 20~40 pg/ml).

The goal of therapy was to achieve clinical improvement and to lower serum cortisol concentration of pre and post ACTH stimulation test (less than 5 μg/dl).

The dog took induction dosage of mitotane (Lysodren; Bristol Laboratories, USA) approximately 25 mg/kg (PO, BID) for 7 days. The mitotane administration was then changed to dosages of 50 mg/kg (PO, SID) for 7 days because the patient did not respond to therapy. In addition, the owner was given prednisolone (2 mg/kg) in case life-threatening hypoadrenocorticism occurred and immediate veterinary care was not available. But iatrogenic hypoadrenocorticism did not occur after medical therapy. Fourteen days after administration of mitotane, the adverse effects were observed including anorexia, vomiting, diarrhea, weakness, and listlessness. As post-ACTH cortisol concentration was controlled approximately after induction treatment with mitotane for 14 days, mitotane administration was changed to 55 mg/kg/week in 2 divided dosages. In addition to mitotane therapy, Silymarin (Sinil Pharm, Korea) and ursodesoxycholic acid (Korea United Pharm, Korea) were prescribed to control markedly elevated hepatic enzymes. The effectiveness of the initial 14 days induction dosage of mitotane was evaluated by means of ACTH stimulation. The results of cortisol concentrations of ACTH stimulation test were that the pre-ACTH cortisol concentration was 0.6, 1.9, 1.0 μg/dl and post-ACTH cortisol concentration was 0.4, 2.2, 0.6 μg/dl in 14 days, 1 month, and 6 months after inducing mitotane therapy, respectively. Appetite, urine volume and frequency were decreased (Fig. 1b). Because serum cortisol concentration was adequately controlled, weekly maintenance dose was continued. ACTH stimulation test was reperformed in 1 month and 6 months after maintenance therapy and the results revealed low serum cortisol concentration.

In dogs with ADH, the autonomous adrenal gland secretion of cortisol turns off pituitary corticotrophin secretion. Thus endogenous corticotrophin should be low to low normal [10].

This finding is consistent with result of this study. Presumably, it may result from the fact that values to be used for test interpretation vary with the laboratory and assay used. In addition, this test is recommended only after a diagnosis of HAC has been established, because dogs with HAC can have a normal endogenous corticotrophin concentration [4,11,12].

HAC is one of the most common endocrinopathies in the dog. The majority of cases are pituitary dependent hyperadrenocorticism (PDH) due to excessive pituitary secretion of ACTH, while 15 to 20% of HAC cases are due to functional adrenocortical adenomas or carcinomas [3]. Complete surgical resection is the treatment of choice for ADH, but surgical adrenalectomy is a difficult procedure and is associated with a high rate of intra- and postoperative complications, including death [8,13]. Approximately half of these tumors are malignant and they have already metastasized by the time of diagnosis in many cases. Thus, medical management is necessary for control of disease, even if adrenalectomy is performed. For these reasons, many veterinarians and owners prefer medical treatment rather than adrenalectomy. Mitotane, the only available drug capable of causing selective, progressive necrosis of adrenal cortex, is considered the treatment of choice for nonresectable or recurrent adrenocortical carcinoma, at least in human beings [6,9]. According to several studies [1,9], mitotane has limited effectiveness in most dogs with cortisol-secreting adrenal tumors, at least when administered at dosages similar to those used in dogs with PDH. In other report [1], a prolonged period of induction (over 2 weeks) was necessary in about 50% of the dogs with adrenal tumors to decrease serum cortisol concentrations satisfactorily [10]. Total induction period in this case was 14 days which was longer than induction period of other PDH cases.

Mitotane is an adrenocorticolytic agent with a direct cytotoxic effect on the adrenal cortex, resulting in selective progressive necrosis and atrophy. Adverse effects of mitotane including anorexia, lethargy, weakness, and diarrhea can occur during treatment period. Thus treatment with mitotane could be discontinued transiently and prednisolone administration could be indicated orally. The dosage of predinisolone is slowly tapered over a period of 2~3 weeks.

A minority (2%) of dogs treated with mitotane showed permanent Addison' disease [1,7]. However, in this case, there was no Addison syndrome-like clinical signs. Reportedly, permanent Addison' disease is usually associated with hyperkalemia, hyponatremia, and low plasma cortisol concentrations before and following ACTH stimulation test. Thus, these dogs often require lifelong mineralocorticoid and glucocorticoid treatment after mitotane therapy [1,7].

The systemic availability of mitotane administered as intact tablets to fasting dogs is poor. One study demonstrated that the availability of mitotane was better with intact tablets given in food and best with ground tablet in oil given in food [1]. The reason for these findings can be explained by the fact that mitotane is a fat-soluble drug. Therefore, we crushed tablets and mixed with oily food.

After ADH was confirmed by HDDST, the induction treatment of mitotane was started at 25 mg/kg/day (PO, BID) for 7 days, and then changed to dosages of 50 mg/kg (PO, SID) for 7 days because the patient didn't respond to therapy. And an ACTH stimulation test showed adequate reduction in adrenal glucocorticoid secretion. Polyuria and polydipsia (PU/PD) and polyphagia were progressively improved. Because post-ACTH cortisol concentration was adequately controlled, the patient was treated on a maintenance schedule of 55 mg/kg of mitotane (every seven days, divided twice). One month after resumption of treatment at the maintenance dose, the ACTH-stimulation test was rechecked and post-ACTH serum cortisol concentration

was well being controlled. The maintenance dosage of mitotane was continued. Gradually hair regrowing, decreased hyperpigmentation and increased skin elasticity were noted.

In this case, the owner declined surgical treatment owing to consideration of the dog's age and the surgical risk, which include high perioperative mortality rates and postoperative complications such as wound dehiscence, infection and thromboembolism. Thus, histopathologic diagnosis and cytologic evaluation of adrenal gland tumor were not performed.

Administration of mitotane is a rational option for treating cortisol-secreting adrenocortical tumors in dog, especially in those with known malignant disease or having severe invasion around tissue. Other report with ADH was recommended with induction dose of 50 to 75 mg/kg/day for 10 to 14 days [10]. In our study, total induction period was 14 days longer than induction period of other PDH cases. According to this result, mitotane therapy is an option as an effective and acceptable alternative to surgery in dog with cortisol-secreting adrenocortical tumors.

Periodical ACTH stimulation test is useful in controlling hyperadrenocorticism of dogs. In addition, to ensure continued control and prevent having a relapse during mitotane treatment, ACTH-stimulation testing should be repeated after 1 and 3 months of mitotane treatment and every 6 months thereafter. At home, the most reliable means that evaluates the effects of mitotane treatment is careful monitoring of the dog's appetite, water consumption and urination frequency. If the owner's intensive care and a periodical cortisol evaluation are achieved, the dog with ADH can be successfully controlled with mitotane therapy.

In conclusion, this case report indicates that a ADH patient with mitotane therapy which is indicated to PDH patients can be managable instead of adrenalectomy.

Acknowledgments

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