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Atypical Cushing's Syndrome Associated with Sex Steroids Excess in a Dog

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Abstract : A 10-year-old, intact male, toy poodle was presented with abdominal distension, truncal alopecia, hepatomegaly, and sustained elevation of alkaline phosphatase. Vacuolar hepatopathy and glycogen deposition in hepatocytes were confirmed by liver biopsy and ultrasound-guided fine-needle aspiration with periodic acid-Schiff (PAS) staining of mass lesion respectively. Cortisol and some sex hormones associated with adrenal gland were analyzed at IDEXX Reference Laboratories before and 1 hour after ACTH stimulation. The results of analysis confirmed elevation of some sex hormones including androstenedione, progesterone and 17 hydroxyprogesterone, not cortisol concentration, before and 1 hour after ACTH stimulation. The dog was diagnosed as atypical form of hyperadrenocorticism associated with sex steroids excess. The treatment was initiated with trilostane (0.5 mg/kg, PO, q12hr) that is an adrenal steroid synthesis inhibitor. Trilostane was administered for 8 weeks and the clinical sign including truncal alopecia was improved.

Key words **:** hyperadrenocorticism, alopecia, atypical Cushing's syndrome, sex steroids.

Introduction

Hyperadrenocorticism, also known as Cushing's syndrome, is one of the most common endocrine disorders of old dogs. Adrenocorticotropic hormone (ACTH) stimulation test with measurement of serum cortisol pre- and post-ACTH injection or low-dose dexamethasone suppression test (LDDST) is required for the diagnosis of hyperadrenocorticism. In some cases, however, the tests performed do not confirm the diagnosis although the clinical signs of patients are similar to hyperadrenocorticism. In these cases, atypical Cushing's syndrome or occult hyperadrenocorticim is diagnosed. The dog with hyperadrenocorticism associated with sex steroid excess often lacks polydipsia and polyuria that is the common clinical signs of classical hyperadrenocorticism (6). In theory, atypical Cushing's syndrome is caused by overproduction of sex hormones instead of cortisol. This syndrome is diagnosed by an ACTH stimulation test with measurement of serum sex hormones including androstenedione, estradiol, progesterone, 17-hydroxy-progesterone, and aldosterone concentrations pre- and post-ACTH (2). Atypical cushing's syndrome is often presented in some specific breeds including miniature poodles. In this case, the patient was diagnosed as hyperadrenocorticism associated with sex steroid excess and well controlled with trilostane therapy.

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Case

A 10-year-old intact male, toy poodle weighing 3.2 kg presented with abdominal distension, alopecia at dorsal region, hepatomegaly and sustained elevation of alkaline phosphatase for 1 year. One month ago, the dog had ureterotomy and nephrotomy to remove ureteral calculi and nephrolith in veterinary medical teaching hospital of Chonbuk National University and there was no history of corticosteroid administration for 6 months recently.

Physical examination revealed the dog was mildly depressed and had mild hypothermia (37.5°C) and respiratory rate was 30 breaths per minute. A complete blood count (CBC) demonstrated mild anemia (packed cell volume (PCV): 35%; reference range, 37-54%). The results of the serum biochemistry analyses revealed increased alkaline phosphatase (ALP) and hypernatremia (6.1 mmol/l; reference range, 3.7 mmol/l - 5.8 mmol/l). The radiographical findings showed hepatomegaly. One month ago, on ultrasonogrphic examination before ureterotomy and nephrotomy, hepatomegaly and a mass (1.43 cm × 1.23 cm) at liver were found. The size of bilateral adrenal gland was normal. Liver biopsy of mass lesion was performed during ureterotomy and nephrotomy. Histopathologic examination of the liver mass identified vacuolar hepatopathy with marked diffuse unclear margin of vacuolation of hepatocytes. At that time, however, the owner did not want to perform any other examination to identify underlying disease causing vacuolar hepatopathy. One month later, the owner wants to treat skin problem with sustained truncal alopecia,

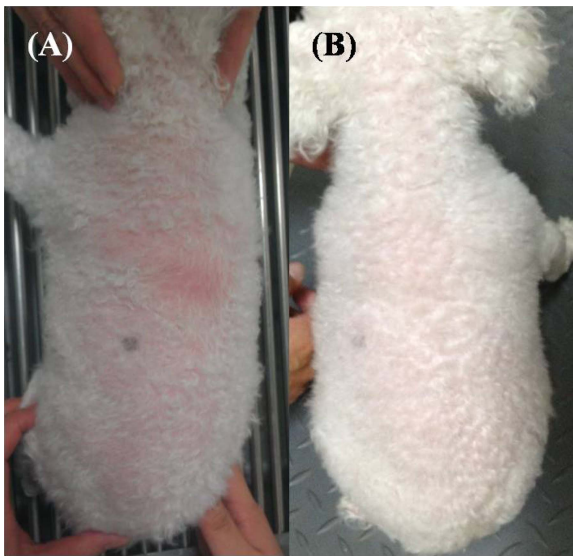

Fig 1. (A) Truncal distribution of alopecia and mild abdominal distension were observed. (B) Truncal alopecia was improved after treatment with trilostane.

abdominal distension, and hepatomegaly (Fig 1A). To confirm morphologic features of liver mass and adrenal gland, ultrasound was performed again. Liver mass and adrenal gland were not changed during one month from ureterotomy and nephrotomy. Ultrasound-guided fine-needle aspiration was performed to stain hepatocytes using a periodic acid-Schiff (PAS) to identify diffuse unclear margin vacuoles of hepatocytes whether these are caused by glycogen deposition or not. Ultrasound-guided fine-needle aspiration (FNA) for cytology of the mass showed a hepatocellular cytoplasmic rarefaction (lesser cytoplasmic density than normal). A PAS staining method was performed to identify cytoplasmic glycogen deposition. The result showed PAS-positive hepatocytes. Hormonal assay were performed to evaluate adrenal function because abnormal adrenal function, hyperadrenocorticism or atypical form of hyperadrenocorticism associated with sex steroids excess, can cause glycogen deposition within hepatocytes. Blood samples were obtained before and 1 hour after ACTH stimulation to measure cortisol and sex hormones concentrations. Blood samples were referred to IDEXX Reference Laboratories (Westbrook, MN, USA). Analysis revealed increased blood androstenedione, progesterone and 17 hydroxyprogesterone before and 1 hour after ACTH stimulation upon presentation (Table 1). However, cortisol concentration was not significantly increased before and 1 hour after ACTH stimulation which was in normal range. Analysis of thyroid hormones was also performed. Decreased total T_4 (0.48 μg/dL; reference range: 1.5 μg/dL to 3.5 μg/dL), free T_4 (0.09 ng/dL; reference range: 1 ng/dL to 2 ng/dL), and thyroid-stimulating hormone (0.01 μU/mL; reference range: 0.03 μU/mL to 0.6 μU/mL) were revealed. Hence, the dog was diagnosed as atypical form of hyperadrenocorticism that producing excessive sex hormone concurrent with decreased thyroid hormone status and treated with trilostane (0.5 mg/kg, PO, q12hr) that is reported to be an adrenal steroid synthesis inhibitor, competitive inhibiting 3-beta hydroxysteroid dehydrogenase resulting reduction of synthesis of cortisol, aldosterone and adrenal androgens. Trilostane was administered for 8 weeks and the clinical sign including truncal alopecia was mildly improved (Fig 1B). Analysis of cortisol and sex steroid hormones was performed after trilostane was administered for 8 weeks. The results showed a reduction in cortisol concentration post-ACTH (from 125.4 ng/mL to 62.9 ng/mL) but an increase in estradiol (from 66.7 pg/mL to 73.8 pg/mL), progesterone (from 2.34 ng/mL to 2.83 ng/mL), 17 hydroxyprogesterone (from 3.88 ng/mL to 7.69 ng/mL) concentration (Table 1).

Discussion

Occurrence of atypical hyperadrenocorticism resulting steroid imbalance is caused equally by adrenal and pituitary tumors unlike classical hyperadrenocorticism that is caused by

Table 1. Comparison of cortisol and some sex hormones concentrations associated with adrenal gland before and one hour after ACTH stimulation

Test	Result (pretreatment)	Result (6 weeks later)	Reference range	Unit
Cortisol (before ACTH stimulation)	40.7	23.1	2.0~56.5	ng/mL
Cortisol (1hr after ACTH stimulation)	125.4	62.9	70.6~151.2	ng/mL
Androstenedione (before ACTH stimulation)	2.15	6.15	0.05~0.36	ng/mL
Androstenedione (1hr after ACTH stimulation)	8.81	7.37	0.24~2.90	ng/mL
Estradiol (before ACTH stimulation)	73.7	89.2	23.1~65.1	pg/mL
Estradiol (1hr after ACTH stimulation)	66.7	73.8	23.3~69.4	pg/mL
Progesterone (before ACTH stimulation)	0.15	0.51	0.03~0.17	ng/mL
Progesterone (1hr after ACTH stimulation)	2.34	2.82	0.22~1.45	ng/mL
17 hydroxyprogesterone (before ACTH stimulation)	0.32	1.6	0.08~0.22	ng/mL
17 hydroxyprogesterone (1hr after ACTH stimulation)	3.88	7.69	0.25~2.63	ng/mL
Aldosterone (before ACTH stimulation)	< 11.0	13.3	11~139.9	pg/mL
Aldosterone (1hr after ACTH stimulation)	91.4	136.1	72.9~398.5	pg/mL

85% have PDH and 15% have adrenal tumors (6).

Cortisol, sex hormones, and aldosterone all are produced in the adrenal gland (9). Most dogs with hyperadrenocorticism (HAC) with classic clinical signs including polyuria and polydipsia, polyphagia, hepatomegaly, a pendulous abdomen, and dermatologic changes including generalized alopecia, skin thinning, and loss of elasticity (7). Dogs with atypical Cushing's syndrome that is caused by sex steroid excess associated with adrenal gland have clinical features suggestive of hyperadrenocorticism but persistently normal or equivocal endocrine test results. The clinical manifestations of a dog with sex steroid imbalance involve some systems such as dermatologic, reproductive, or hepatic. Atypical form of HAC often lacks the classical clinical signs of HAC including polydipsia and polyuria because of the lack of hypercortisolemia (6). Dogs with sex steroid excess may exhibit dermatologic manifestations including truncal hair loss and hyperpigmentation as the only clinical sign without any other signs of classical HAC (4,6,8). Alopecia of atypical HAC is seen more frequently in miniature poodles, chow chows, Pomeranians, and arctic breeds such as Samoyeds, elkhounds, and Alaskan malamutes (6). Reproductive signs of excessive adrenal sex hormone can include perianal adenoma that is most common manifestation of sex steroid excess in a female or castrated male, clitorial hypertrophy in females, behavioral estrus in female dogs or cats, testicular atrophy in intact males, prostatomegaly in male castrated dogs, or behavioral and physical signs of testosterone excess including mounting behavior, penile barbs in cats (6). The most common serum chemistry abnormalities associated with sex steroid excess is elevation of alkaline phosphatase (ALP) and alanine transferase (ALT) and this is the most common cause of presented to hospital (6). Most dogs with classical hyperadrenocorticism have positive results with ACTH stimulation test, low-dose dexamethasone suppression test (LDDST). However, some dogs have negative results with these tests, although clinical signs were suggestive of this disease. Traditionally, HAC is thought of as a disease in which excess cortisol or ACTH is produced in adrenal tumor and pituitary-dependent hyperadrenocorticism respectively. However, negative cortisol changes on both ACTH stimulation and LDDST are revealed in atypical form of HAC (9). Dogs with sex steroid excess may have negative ACTH stimulation and LDDS tests because atypical form of HAC may be due to excess cortisol precursor including 17-hydroxyprogesterone, androstenedione, testosterone not cortisol. In these dogs, serum cortisol concentrations are normal (5,9). The ACTH stimulation test with measurement of cortisol precursor including 17-hydroxyprogesterone, androstenedione, and testosterone is the test for diagnosis of adrenal sex steroid excess (6). Basal cortisol and sex hormone concentration are not reliable for diagnosis of adrenal dysfunction including HAC and atypical form of HAC (1-3). Increased sex hormones have been reported in Pomeranians and Chows caused by an adrenal hyperplasia-like syndrome mediated by a deficiency of 1 enzyme (usually 21 hydroxylase) (9). Schmeitzel and Lothrop hypothesized the alopecia associated with sex hormone excess was due to a partial deficiency of 21-hydroxylase, an enzyme needed for cortisol synthesis (10). Because this patient had normal serum cortisol concentration, the deficiency of 21-hydroxylase was assumed to be partial (2).

Dogs with PDH and atypical form of HAC will often show changes in thyroid hormone status that is decreased basal thyroxine (T_4) and triiodothyronine (T_3) caused by euthyroid sick syndrome and decreased endogenous thyroid-stimulating hormone (TSH) secretion caused by overcrowding of pituitary thyrotrophs (11). In this case, decreased thyroid hormones including total T4, free T4, and thyroid-stimulating hormone were revealed.

There are three treatment options for canine HAC and adrenal sex steroid excess. Medical therapy using mitotane, ketoconazole, L-deprenyl, and trilostane, surgical therapy that is unilateral adrenalectomy, and radiation therapy are used. Among medical therapy, trilostane that is competitive inhibitor of 3-beta-hydroxysteroid dehydrogenase, the enzyme that mediates the conversion of pregnenolone to progesterone may be an alternative to mitotane therapy for HAC in dogs, particularly those suffering from sex steroid imbalance (6). In one report, a dog that had a negative ACTH stimulation test and a negative LDDST on the basis of cortisol response was treated with trilostane. The dog was improved all clinical signs associated with HAC. Analysis of sex steroid horome, however, was showed a decrease in cortisol and an increase in hydroxyprogesterone concentration post-ACTH administration and hydroxyprogesterone did not appear to be a useful marker for monitoring response to this drug (9). In this case, there was no reduction of sex steroid hormone such as 17 hydroxyprogesterone. However, the result showed reduced cortisol concentration after ACTH stimulation test compared with before treatment using trilostane. In another report, the author stated that serum sex hormone concentrations did not change significantly or may be elevated in response to treatment although clinical signs were resolved (2).

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개에서 발생한 성호르몬 과다 분비와 관련된 비정형 부신피질기능 항진증

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요 약 : 10년령의 수컷 푸들이 복부팽만, 등쪽 몸통 부위 탈모, 간비대와 혈청 알칼리인산분해효소의 지속적인 상승으로 전북대학교 수의과대학 동물병원에 내원하였다. 간 생검 및 미세침흡인세포 검사법과 PAS 염색을 실시한 결과 공포성 간병증 및 간세포에 글리코겐이 침착된 것을 확인 하였다. ACTH 자극 시험 실시 전 후 코티솔 및 부신과 관련된 성 호르몬의 농도를 측정하였다. 측정결과 안드로스텐디온, 프로게스테론 및 수산화 프로게스테론의 상승을 관찰할 수 있었으며 코티솔농도는 정상 범위내에 존재하였다. 진단은 성호르몬과 관련된 비정형의 부신피질 기능 항진증으로 내렸으며 치료는 트릴로스탄으로 하였다. 치료 8주 후 등 부위의 탈모를 포함한 임상증상들이 개선되었다.

주요어 : 부신피질 기능 항진증, 탈모, 비정형 쿠싱, 성호르몬