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Mitotane Therapy and Management of Naturally Occurring Pituitary Dependent Hyperadrenocorticism (PDH) in a Dog

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Abstract : A 10 year old, intact female Yorkshire terrier was referred to the Veterinary Teaching Hospital of Konkuk University. Upon admission, the patient had severe necrotic skin disease on face and abdominal wall, and also showed polyuria, polydipsia (PUPD), and polyphagia. A tentatative diagnosis of hyperadrenocorticism was made on the basis of history takings, physical examination, and results of CBC and serum biochemistry. Hyperadrencorticism was confirmed by ACTH stimulation test and pituitary-dependent hyperadrenocorticism (PDH) was diagnosed according to the results of high dose dexamethasone suppression test (HDDST). After initiating mitotane therapy, severe skin problem and clinical signs including PUPD were improved. And we determined whether or not mitotane therapy well controlled serum cortisol level with ACTH stimulation test. This case was presented to show that the patient misdiagnosed and treated for more than 1 year as other dermatologic problems in 3 local animal clinics was treated and managed successfully with mitotane administration.

Key words **:** hyperadrenocorticsm, dog, mitotane

Introduction

Hyperadrenocorticism is caused by the excessive secretion of cortisol from the adrenal cortex and is a common endocrine disorder in dogs. Approximately 85% of dogs with hyperadrenocorticism results from excessive secretion of adrenocorticotropic hormone (ACTH) from pituitary gland.[7] Adrenocortical neoplasm (adenoma or adenocarcinoma) autonomously secretes an excessive quantity of cortisol independent of endogenous corticotropin control. There are three treatments commonly used in the management of PDH in dogs. Mitotane (o,p-DDD), ketoconazole, and L-deprenyl can produce satisfactory result in dogs with PDH.[1]

Of three treatments, o,p-DDD (mitotane) has been used commonly in the treatment of hyperadrenocorticism. In addition, mitotane is a patent adrenocorticolytic agent, causing necrosis of adrenal cortex (zona fasiculata and reticularis) to decrease cortisol level in serum. Clinical signs of hyperadrenocorticism include polyuria/polydipsia (PUPD), alopecia, polyphagia, lethargy and muscle weakness. In addition, panting and abdominal enlargement are typical signs.[7] The purpose of this case report is to present that the patient misdiagnosed and treated for more than 1 year as other dermatologic problems was treated and managed successfully with mitotane therapy and a periodical ACTH stimulation test is important to monitor responsiveness to mitotane therapy in Cushing's disease.

Case Presentation

Case history

A 10-year-old, intact female Yorkshire terrier was referred to the Veterinary Teaching Hospital of Konkuk Univerinary with 8-month duration of endocrinological and dermatological problems, such as polyuria, polydipsia and polyphagia.

Physical examination

The abnormal physical findings at presentation were necrotic dermatitis, alopecia (Fig. 1), dry ear wax, patella luxation, and bilateral cataract.

Complete blood counts (CBC) and serum chemistry, urine culture and urinalysis

The hemogram revealed polycythemia and thrombocytosis. Abnormal serum chemical findings were hypertriglyceridemia, hyperproteinemia, hyperalbuminemia, and low calcium level. Results of urinalysis revealed struvite crystals and glucosuria.

Pustular bacterial culture

Results of bacterial culture were positive and *Staphylococcus intermedius* was isolated.

Radiography and Ultrasonography

There were enlarged liver, gas filled small intestine on abdominal radiography and mild tracheal collape, enlarged caudal vena cava on thoracic radiography.

Fungal culture

Fungal culture with both dermatophyte test medium (DTM) and Sabourauds dextrose agar (SDA) were negative.

Diagnosis

A tentative diagnosis of hyperadrenocorticism was made on the basis of history, physical examination radiograph, and result of hemogram and serum biochemical testing.

Naturally occurring hyperadrenocorticism was confirmed by distinct increase in serum cortisol concentration 1 hour

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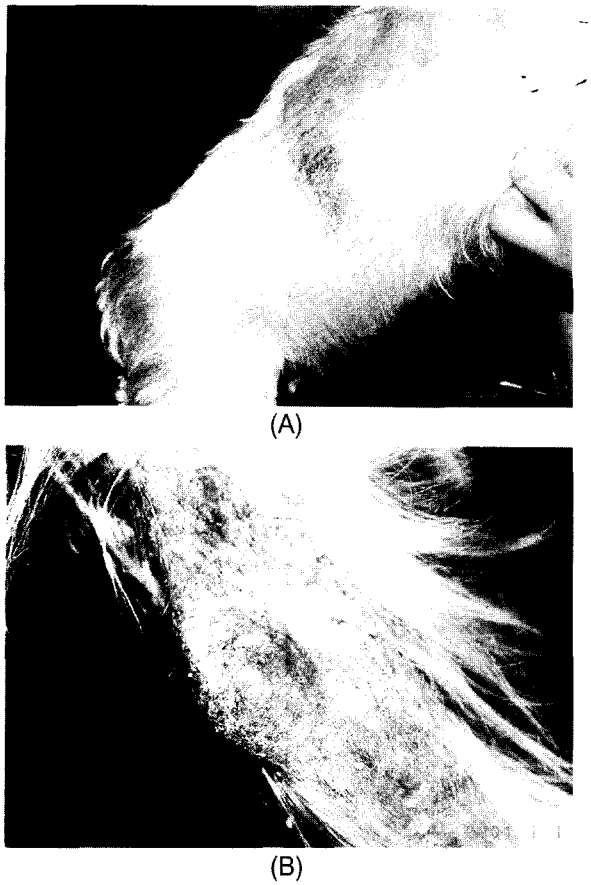

Fig 1. The abnormal physical finding at presentation was necrotic dermatitis, alopecia (A and B).

after administration of ACTH (Synacthen®, 0.25 mg, IM) (Table 1).

Then pituitary-dependent hyperadrenocorticism was diagnosed on the basis of high dose dexamethasone suppression test, collecting serum 4 and 8 hours after administration of a high dosage of dexamethasone (1.0 mg/kg, IV), (Table 2).

Table 1. Results of ACTH stimulation test in suspected naturally occurring hyperadrenocorticism patient

Items tested	Concentration of cortisol(μg/dl)
Cortisol(pre-ACTH)	3.4
Cortisol(post-ACTH)	27.8

Table 2. Results of high dose dexamenthasone suppression test in naturally occurring hyperadrenocorticism patient

Items tested	Concentration of cortisol (μg/dl)
Cortisol(pre-dexamethasone)	4.6
Cortisol(4 hour after administration)	0.6
Cortisol(8 hour after administration)	0.6

Treatment and management

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 was given an induction dosage of mitotane of approximately 50 mg/kg(PO, SID) for 10 days. In addition, the owner was given prednisolone (2 mg/kg) in case sign of life-threatening hypoadrenocorticism occured and immediate veterinary care was not available. The adverse effects most commonly observed include anorexia, vomiting, diarrhea, weakness, or listlessness.

If post-ACTH cortisol concentration is controlled appropriately after induction treatment with mitotane for 10 days, mitotane administration was changed to a maintenance dosage of appropimately 50 mg/kg/week given in two divided doses. In addition to mitotane therapy, antibiotics (ciprofloxacin) was prescribed on basis of antibiotics sensitivity test result against skin problem and antifungal (chlorhexidine) shampoo was indicated for the prevention of secondary fungal infection.

The effectiveness of the initial 10 days induction dosage of mitotane was evaluated by means of an ACTH stimulation test (Table 3). The patients appetite, urination volume and frequency was decreased and dermatoligical problems was improved (Fig. 2).

Because serum cortisol concentration was adequately controlled, maintenance weekly dosage was continued, divided into 2 doses. After maintenance therapy (for 3 months) with mitotane, ACTH stimulation test was conducted and the results revealed high serum cortisol concentralion after ACTH administration (Table 4). In addition, the patients appetite

Table 3. Results of ACTH stimulation test in naturally occurring pituitary-dependent hyperadrenocorticism patient after induction mitotane therapy

Items tested	Concentration of cortisol(μg/dl)
Cortisol(pre-ACTH)	0.6
Cortisol(post-ACTH)	0.4

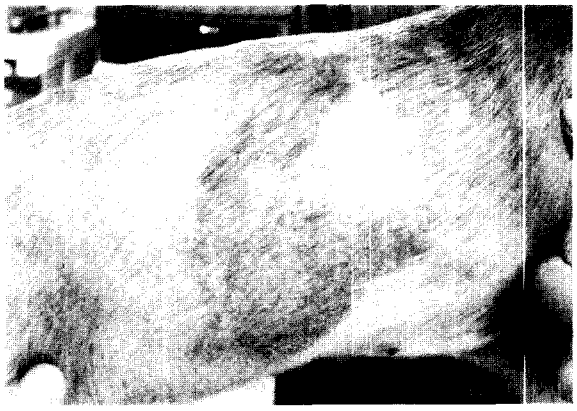

Fig 2. Hair was regrown in a dog with naturally occurring pituitary dependent hyperadrenocorticism after mitotane therapy.

Table 4. Results of ACTH stimulation test in naturally occurring pituitary-dependent hyperadrenocorticism patient after 3-month maintenance therapy

Items tested	Concentration of cortisol(μg/dl)
Cortisol(pre-ACTH)	3.2
Cortisol(post-ACTH)	15.0

Table 5. Results of ACTH stimulation test in naturally occurring pituitary-dependent hyperadrenocorticism patient after an increased mitotane therapy

Items tested	Concentration of cortisol(μg/dl)
Cortisol(pre-ACTH)	1.0
Cortisol(post-ACTH)	0.6

was increased and skin condition was slightly worse than 3 months ago.

Because cortisol concentration of post-ACTH was high, the patient was given an increased dosage(40 mg/kg/day, PO, SID, for 7 days) of mitotane. After adminiatration of an increased dosage of mitotane, ACTH stimulation test was reconducted and the results revealed that post-ACTH serum cortisol concentration was low (Table 5).

Discussion

Cushing's syndrome or hyperadrenocorticism is one of the most common canine endocrinopathies. The clinical signs are caused by persistent elevation of serum cortisol level. Hyperadrenocorticism consists of pituitary-dependent hyperadrenocorticism and adrenal tumor. Approximately 85% of dogs with cushing's syndrome result from excessive secretion of ACTH from pituitary gland. Adrenal tumor, which account for the remaining 15% of hyperadrenocorticism, secretes cortisol autonomusly.[3,7]

Pituitary-dependent hyperadrenocorticism includes a pituitary tumor secreting excess adrenocorticotropic hormone (ACTH) with secondary adrenocortical hyperplasia and pituitary hyperplasia caused by excesses in corticotropin releasing hormone (CRH) secretion due to hypothalamic disorder. Dogs with PDH are usually older than 6 years of age, more than 75% are older than 9, and their median age is 11 years. Dogs with hyperadrenocorticism caused by functioning adrenocortical tumors tend to be older than those with PDH.

O,p'-DDD, ketoconazol and L-deprenyl can be used for hyperadrenocorticism. Among these agents, Mitotane is an adrenocorticolytic agent with a direct cytotoxic effect on the adrenal cortex, resulting in selective progressive necrosis and atrophy.[1] In addition, ketoconazol lowers the circulating cortisol concentration by enzymatic inhibition of steroid biosynthesis.

In dogs dopamine primarily seems to inhibit the secretion of corticotropine peptides from the pars intermedia and it may also affect corticotropine release from the pars distalis.[1] L-deprenyl, selegiline HCl, is a selective and irreversible inhibitor of monoamine oxidase type B that helps to restore the central dopamine concentration and facilitates dopaminergic transmission by several mechanism.

Adverse effects of mitotane including anorexia, lethargy, weakness, and diarrhea can be occurred during treatment period. And then treatment with mitotane transiently should be discontinued and prednisolone administration is indicated orally. The dosage of prednisone is slowly tapered over a period of 2~3 weeks. In case that prednisone is discontinued and the dog is stable without additional treatment, mitotane is again given at a lower dosage. According to the reports[1,5], a minority (2%) of dogs treated with mitotane showed permanent Addison's disease. However, in this case, there was no Addison-like syndrome. Reportedly, permanent disease is usually associated with hyperkalemia. Hyponatremia, and low plasma cortisol concentrations before and following ACTH stimulation test. Thus, these dogs often require lifelong mineral corticoid and glucocorticoid treatment[1,5].

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 diet food.

After PDH was confirmed by high dose dexamethasone suppression test (HDDST), the induction treatment of mitotane was started at 50 mg/kg/day (PO, SID) for 10 days, and an ACTH stimulation test showed adequate reduction in adrenal glucocorticoid secretion(Table 3). Polyuria and polydipsia(PUPD) and polyphagia were improved, but skin problem was not dramatically improved.

Because post-ACTH cortisol concentration was adequately controlled, the patient was treated on a maintenance schedule of 50 mg/kg of o,p-DDD(every seven days, two divided). Seven days after resumption of treatment at the maintenance dose, there had been the decreased appetite, water intake, urine volume, and a distinct improvement of skin problem was noted. In addition, the multifocal papules and exudates were decreased.

Seventy days after that therapy, there was no increased appetitie and polyuria and hair regrowth was observed. However 80 days after treatment with mitotane, the dog had dermatological problems (multifocal alopecia on the back) in addition to initial lesion. Also, the owner complained of PUPD and increased appetite. The ACTH-stimulation test was reexamined, and high post-ACTH serum cortisol concentration was noted. Thus, the induction treatment with mitotane was started again [40mg/kg/day SID, PO, for 7days]. The ACTH stimulation test was reevaluated, indicating good serum cortisol level (Table 5). The maintenance dosage(55mg/kg per week in two divided doses) of mitotane was continued. Seven days after resumption of treatment at elevated maintenance dose, PUPD and skin problems were

improved dramatically, ie hair regrowth, decreased hyperpigmentation and increasd skin elasticity.

Conclusions

In conclusion, because clinical improvement is direct relation to cortisol concentration in serum, this study demonstrates that 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 3 and 6 months of mitotane treatment and every 6 month thereafter. At home, the most reliable means that evaluates the effects of mitotane treatment is careful monitoring the dogs appetite, urine volume and urination frequency. If the owners intensive care and a periodical cortisol evaluation are achieved, the dog with PDH can be successfully controlled with mitotane therapy.

Acknowledgments

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개에서 자연발생한 뇌하수체 의존성 부신피질기능 항진증의 치료 및 관리

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요 약 : 10년령의 중성화 되지 않은 암컷의 요크셔테리어가 건국대학교 부속 동물병원으로 진료가 의뢰되어 왔다. 환축은 얼굴과 복벽에 심각한 괴사성 피부염을 보였으며 또한 다음다뇨 및 다식증을 나타내었다. 병력청취와 신체검사, CBC, 혈액생화학 검사를 토대로 하여 부신피질기능항진증을 의심하였고, 나아가 ACTH 자극시험을 통하여 쿠싱증후군이 확진되었다. 또한, High Dose Dexamethasone Suppression Test (HDDST)를 통하여 뇌하수체 의존성 부신피질기능 항진증임을 알 수 있었다. Mitotane을 이용한 치료가 개시된후 심각한 피부문제와 PUPD 등의 임상증상들이 개선되었다. 그 후 mitotane 처치가 적절히 이루어지고 잇는가를 검증하기 위해 ACTH의 추가적인 검사가 수행되었다. 이 임상증례는 심각한 피부문제를 가지고 있던 환축이 오진단되고 치료의 핵심을 찾지못해 1년 이상 지속된 환축이 mitotane을 이용하여 성공적으로 치료되어 유지되고 있음을 보여주는 증례이다.

주요어 : 부신피질기능항진증, 개, mitotane