Original

Clinicopathologic and Morphologic Analysis of the Adrenal Gland in Pomeranians with Non-Illness Alopecia

全身症状を伴わない脱毛症を呈したポメラニアンにおける副腎の臨床病理学および形態学的検討

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Abstract: We performed MRI scanning of the adrenal glands together with both clinicopathologic analysis and a skin biopsy in Pomeranians with non-illness, generalized alopecia. Fifty-one Pomeranians with the alopecia were included in this study, all of which had a brachycephalic type. Laboratory tests carried out on selected cases revealed slight elevations of several tests PCV, ALT, AST, ALP, and blood glucose, a slightly exaggerated response to ACTH stimulation test, and in some cases, inadequate suppression against low-dose dexamethasone. All animals showed a normal response to TSH administration. All 18 dogs on which we performed skin biopsies showed mild epidermal thinning, hyperkeratosis, follicular atrophy, and thinning of the subcutaneous adipose tissue. MRI scanning was performed in 14 of the affected dogs and 3 healthy control Pomeranians. Median length, width, and thickness of the adrenal gland in affected dogs were not different from those in control dogs, and no abnormality of the pituitary gland was found. Based on these findings, it is considered that abnormal adrenal steroidogenesis associated with adrenal hyperplasia is not an acceptable pathogenesis of this condition. It is hypothesized that the affected dogs seem to have a breed- and/or family-specific, physiological hormonal constitution that may lead to alopecia, rather than suffering from a functional anomaly of the adrenal gland.

Key words: alopecia, dog, MRI

要 約: 全身症状を伴わない汎発性脱毛症のポメラニアンに対して、臨床病理学および皮膚病理組織学的検討と共に副腎のMRI検査を実施した。罹患例51例を本試験に供したが、全例が短頭種型であった。諸検査を施行し、一部の症例でPCV, ALT, AST, ALP, 血糖の軽度上昇, ACTH負荷試験による軽度の過反応, 低用量デキサメタゾン抑制試験における抑制障害がみられた。TSH刺激試験に異常はみられなかった。皮膚病理組織学的検査施行18例すべてで軽度の表皮萎縮, 角質肥厚, 毛包萎縮, 皮下脂肪組織の肥厚がみられた。MRI検査を罹患例14例と健常犬3例に施行したが、両者に副腎の平均長径, 短径, 厚さの差異を認めず, 下垂体異常もみられなかった。以上より, 副腎過形成を誘導する副腎ステロイド合成異常の病因的関与は否定的と考えられた。本症罹患犬は, 先天的副腎機能的異常よりも, 全身症状を発症しない脱毛症を呈す種もしくは家系特異的な生理学的ホルモン素因を有していると推察された。

キーワード: 脱毛症, 犬, MRI

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INTRODUCTION

Siegel¹¹⁾ coined the term “Pseudo-Cushing’s Syndrome” for idiopathic non-illness, generalized alopecia, which is similar to Cushing’s syndrome in dogs. The syndrome occurs most commonly at 1 to 2 years of age, especially in male Pomeranians with no remarkable abnormalities in hemogram, serum chemistry analysis, or urinalysis^{6,9)}. Some veterinary dermatologists call this phenomenon alopecia X, since the etiology remains unknown^{1,8)}. In the 1990s, it was speculated that a deficiency of 21-hydroxylase, an enzyme involved in adrenal steroidogenesis, was involved and this condition gave rise to the name congenital adrenal hyperplasia-like syndrome⁷⁾. It is suspected that an excess of sex hormone is due to the loss of cortisol negative-feedback regulation of ACTH secretion, resulting in a chronic excess of ACTH leading the enlarged adrenal glands. To date, however, there have been no morphologic studies of the adrenal gland in dogs with the alopecia, even though it is considered that abnormal adrenal steroidogenesis could be involved in the pathogenesis¹⁾.

The purpose of this study is to evaluate morphologic verification of adrenal hyperplasia in Pomeranians with alopecia. We performed magnetic resonance imaging (MRI) scanning of the adrenal glands together with both a clinicopathologic analysis and a skin biopsy in the dogs.

MATERIALS AND METHODS

Cases

Fifty-one Pomeranians clinically diagnosed with the alopecia were included in this study. All cases were referred with a history of chronic, symmetrical alopecia, especially in the neck, trunk, caudal thigh, and tail, without any systemic signs (Fig. 1A).

Of the 51 dogs, 31 (60.8%) were intact males, 7 (13.7%) were castrated males, 9 (17.6%) were intact females, and 4 (7.8%) were spayed females. Their ages varied from 1 to 10 years, with a mean age of 4.3 years, and the mean age at which their owners noted a hair-coat abnormality was 3.1 years. Interestingly, all affected Pomeranians showed a brachycephalic face, which is characterized by a shorter length of the nose bridge compared with control dogs (Fig. 1B).

A

B

Fig. 1. Clinical features of affected Pomeranians. Note symmetric alopecia except for the face and distal extremities, and short nose-bridge (A), compared with control dogs (B).

Clinicopathologic analysis

Several laboratory tests were carried out on selected cases; hemograms including red blood cells, hemoglobin, packed cell volume (PCV), white blood cells, and platelet counts in 35 cases, and serum chemistry analysis including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen, creatinine, blood glucose, cholesterol, total protein, albumin, globulin, calcium, phosphate, sodium, potassium, and chlorine in 41 cases. In addition, we performed an adrenocorticotrophic hormone (ACTH) stimulation test in 19 cases, a low-dose dexamethasone (LD) suppression test in 19, and a thyroid-stimulating hormone (TSH) stimulation test in 20, hormonal functional tests were performed using standard procedures³⁾. In the ACTH stimulation test, less than 22 $\mu\text{g}/\text{dl}$ of cortisol values at the 1st hour were considered normal. In the LD suppression test, less than 1.4 $\mu\text{g}/\text{dl}$ of

Fig. 2. Results of ACTH stimulation tests in affected dogs. Four of 19 cases (21%) had a slightly exaggerated response.

cortisol value at the 8th hour were also considered normal, as well as TSH stimulation tests showing less than 3.0 $\mu\text{g/dl}$ of T4 value or twice T4 value compared with a baseline level at the 6th hour.

Histopathology of the skin

Skin biopsies were performed for the alopecia in 18 cases. Tissue specimens were taken with 6-mm punch biopsies, fixed in neutral buffered 10% formalin, and processed using standard procedures.

MRI Scanning

MRI (Flexart: MRT-50GP, Toshiba, Tokyo, Japan) was performed for 14 Pomeranians with the alopecia and 3 healthy controls the dogs were positioned in sternal recumbency. Sagittal, horizontal, and transversa sections were obtained through the adrenal glands and the pituitary fossa. The Images were obtained of T1 & T2- weighted, 4-mm contiguous sections. Size of the adrenal glands was estimated by measuring the maximum length, width,

Fig. 3. Results of LDD suppression tests in affected dogs. Ten of 19 cases (53%) had inadequate suppression.

and thickness, with particular attention also given to the presence or absence of a pituitary mass.

RESULTS

Clinicopathologic analysis

Hemograms revealed a slightly elevated PCV (median 57, range 56–58) in 6 of 35 dogs (17%). In serum chemistry analysis, the most common findings were a mild elevation of ALT (median 190 U/l, range 134–299 U/l) in 15 of 40 cases (38%), AST (median 59 U/l, range 44–87 U/l) in 7 of 20 (35%), ALP (median 510 U/l, range 258–1336 U/l) in 13 of 40 (32%), and blood glucose (median 134 mg/dl, range 127–149 mg/dl) in 12 of 34 (35%). The remaining tests showed no abnormalities. Figures 2 and 3 showed results of the hormonal functional tests. Four of 19 cases (21%) had a slightly exaggerated response to the ACTH stimulation test (median 24.6 $\mu\text{g/dl}$, range 22.6–27.8 $\mu\text{g/dl}$), and 10 of 19 (53%) showed inadequate suppression in the LD suppression tests (median 3.1 $\mu\text{g/}$

Fig. 4. Histopathologic features of the skin. Note mild epidermal thinning, hyperkeratosis, and follicular atrophy. In addition, subcutaneous adipose tissue was thicker than in the dermis.

dl, range 1.5–9.2 $\mu\text{g/dl}$). All cases had a normal response to TSH administration.

Skin histopathology

In all cases, histopathologic findings revealed mild epidermal thinning, hyperkeratosis, and follicular atrophy consistent with the telogen stage. In addition, the subcutaneous adipose tissue was thicker than that in the dermis (Fig. 4).

MRI Scanning (Fig. 5 and Table 1)

The left adrenal gland was clearly visible, whereas it was difficult to find the right adrenal gland due to an anatomical overlap by the caudal vena cava. The median length (13 mm-left, 12 mm-right), width (4 mm-left, 4 mm-right), and thickness (5 mm-left, 5 mm-right) of the adrenal gland in the dogs with the alopecia were very similar to the median length (13 mm-left, 12 mm-right),

A

B

Fig. 5. MRI scanning of the adrenal (A) and pituitary gland (B). There are no morphologic abnormalities.

width (4 mm-left, 5 mm-right), and thickness (6 mm-left, 6 mm-right) in control dogs. In addition, no cases showed any mass corresponding to hyperplasia or a tumor of the pituitary gland.

DISCUSSION

In this study, adrenal hyperplasia was not detected morphologically in Pomeranians with alopecia. Congenital adrenal hyperplasia is an endocrinologic disorder recognized in human neonates, and takes two forms: a simple virilizing or a salt-wasting form⁵⁾. Female patients are usually virilized, whereas affected males are normal in appearance⁵⁾. About two thirds of patients have mineralocorticoid deficiency, and the salt-wasting form results in hypoaldosteronism⁵⁾. The present Pomeranian alopecia was male-predisposed, and the dogs showed no systemic signs, even though increases in 17-hydroxyprogesterone and cortisol production have been suggested^{1,7)}. A recent genetic study showed that no

Table 1. MRI measurements of adrenal glands in 14 Pomeranians with alopecia and in 3 healthy controls

Cases	Left adrenal gland (mm)			Right adrenal gland (mm)		
	length	width	thickness	length	width	thickness
1	12	4	6	13	4	6
2	11	4	5	13	4	4
3	10	4	6	12	6	–
4	14	4	5	12	–	–
5	14	4	6	–	–	–
6	13	4	5	–	–	–
7	11	4	5	–	–	–
8	11	6	–	10	4	6
9	13	5	–	9	3	–
10	13	3	–	9	4	–
11	13	4	–	–	–	–
12	13	3	–	–	–	–
13	12	6	–	–	–	–
14	16	–	–	14	–	–
Control dogs						
1	11	3	6	12	5	–
2	14	4	–	–	–	6
3	14	4	–	–	–	–

–; Not visible.

mutation of the 21-hydroxylase genes was found in the affected Pomeranians¹²⁾. Based on these findings, abnormal adrenal steroidogenesis associated with adrenal hyperplasia is not an acceptable pathogenesis of this condition. Some investigators have postulated that this is a breed-associated mild form, or a variant of pituitary-dependent hyperadrenocorticism¹⁾. However, it should be emphasized that these dogs displayed only aesthetic problems, that start just after adolescence without any metabolic disturbance. In this study, all affected Pomeranians showed characteristic facial shape along with a slightly exaggerated response to ACTH stimulation test and, in some cases, inadequate suppression upon undergoing LD suppression tests. Thus, it is hypothesized that the dogs seemed to have a breed- and/or family-specific, physiological hormonal constitution, which might lead to non-illness alopecia and the above characteristic facial structure rather than suffering from a functional anomaly of the adrenal gland.

As for its dermatological aspects, the distribution of the alopecia is restricted to specific areas such as the cervix, trunk, tail, perineal area, and caudal thigh, but the face and distal extremities are always spared⁹⁾. In addition,

hair re-growth at injured sites (e.g. biopsy, trauma, and dermatitis) is one of common features in such dogs¹⁰⁾. These clinical characteristics suggest that a local defect in the hair growth cycle could be involved in the pathogenesis, and that the alopecia of Pomeranians might involve a similar physiologic process to that in human androgenic alopecia, which is a genetically predisposed, male-predominant, early-life onset, and a non life-threatening follicular dysfunction^{2, 4)}. Further investigations will be needed.

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