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**DOMESTIC  
ANIMAL  
ENDOCRINOLOGY**

Case report

## Acromegaly due to a somatroph adenoma in a dog

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### Abstract

A 10-year-old uncastrated male Dalmatian dog was referred for gait abnormalities consisting of chronic progressive stiffness and rigidity. Other symptoms were polyphagia associated with weight gain, polyuria and polydipsia, excessive panting, and an inspiratory stridor. The owner had noticed progressive thickening of the skin and enlargement of the tongue over the last 3 years. Physical examination revealed thickening of the skin, redundant skin folds, and enlargement of the tongue. The only remarkable abnormalities found on routine laboratory examination were mild anaemia and an increased serum fructosamine concentration. Circulating concentrations of total thyroxine, free thyroxine, and cTSH, and the results of an ACTH stimulation test were all within reference ranges. The basal serum growth hormone (GH) concentration was markedly elevated (23 µg/l) and did not decrease during a glucose tolerance test or after somatostatin administration. The serum insulin-like growth factor-1 concentration was also markedly elevated (1254 µg/l). Basal serum insulin concentration was high (95 mU/l) and insulin concentrations increased considerably after glucose loading, consistent with insulin resistance. Abdominal ultrasonography showed no abnormalities.

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Survey radiographs of the vertebral column showed severe spondylosis deformans extending from the cervical to the lumbosacral spine. CT scanning of the skull showed an enlarged pituitary gland with normal enhancement pattern. On post-mortem examination, the entire vertebral column appeared as a single and inflexible structure due to the presence of multiple fused osteophytes. The pituitary gland contained an acidophilic adenoma that immunostained positively for GH (and negatively for ACTH and alpha-MSH).

In conclusion, this Dalmatian dog with acromegaly and insulin resistance represents the first case of GH hypersecretion proven to be due to a somatotroph adenoma.

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*Keywords:* Canine; Pituitary; Insulin-like growth factor-1; Growth hormone

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## 1. Introduction

Acromegaly is a chronic syndrome, characterized by overgrowth of connective tissue, bone, and viscera due to growth hormone (GH) hypersecretion in adulthood. This syndrome is known to occur in humans, dogs, and cats, but the pathogenesis differs completely in these species. In humans and cats, the excessive GH secretion is caused by a somatotroph adenoma of the pituitary gland [1,2]. In dogs, the GH excess originates from an extra-pituitary site [3]. In female dogs either endogenous progesterone (metoestrus) or exogenous progestins (used for oestrus prevention) may give rise to hypersecretion of GH in the mammary gland, resulting in acromegaly and glucose intolerance [3–5].

So far, there is no conclusive evidence that pituitary tumours give rise to GH hypersecretion in dogs. There are two reports of pituitary tumours, one in a 9-year-old male English Bulldog with thickened cranial bones [6], and one in a 5-year-old male Boston Terrier with diabetes mellitus supposedly due to GH excess [7]. In both cases, GH hypersecretion was not demonstrated and immunohistochemistry of the pituitary tumours was not performed. More recently, immunohistochemical staining for GH revealed a somatotroph adenoma in a 9-year-old male Doberman Pinscher with severe insulin-resistant diabetes mellitus [8]. However, no acromegalic features were observed and circulating levels of GH and insulin-like growth factor-1 (IGF-1) were not measured.

Here we report on the physical, endocrine and (histo)pathological findings in a male dog with acromegalic changes and insulin resistance due to a GH-secreting pituitary adenoma. To the authors' knowledge, this case report is the first description of excessive GH secretion due to a somatotroph adenoma in a dog.

## 2. Material and methods

### 2.1. Sample collection and endocrine tests

Blood samples were collected by veinpuncture and transferred to plain serum tubes, which were left at room temperature for a minimum of 45 min and maximum of 1 h prior to

centrifugation and serum harvesting. Samples were stored at  $-20^{\circ}\text{C}$  until assayed. Samples for GH determination were sent on dry ice by courier from Bologna to Utrecht.

The glucose tolerance test was performed by giving 50% glucose solution intravenously (1 g/kg body weight) and measuring concentrations of GH, insulin, and glucose at 0, 15, 30, 60, and 90 min after glucose administration. The glucose disappearance coefficient ( $K$ ) was calculated according to  $K = 69.3/t^{1/2}$  glucose = % elimination rate/min [9].

The somatostatin suppression test was performed by collecting blood samples for measurement of the GH concentration at  $-15$ , 0, 15, 30, 45, 60, and 90 min after the intravenous administration of 10  $\mu\text{g}$  somatostatin [Somatostatina<sup>®</sup>; I.B.P. Pharma, Italy] per kg body weight.

## 2.2. Hormone determination

Serum cortisol concentrations were measured by a competitive immunoassay (Immulite<sup>®</sup> Cortisol, Diagnostics Products Corporation, Los Angeles, USA). The intra-assay coefficients of variation were 10.0% and 6.3% at cortisol levels of 74 and 524 nmol/l, respectively. The sensitivity of the assay was 5.5 nmol/l.

Serum GH concentrations were measured by a homologous radioimmunoassay (RIA) as described by Eigenmann and Eigenmann [10]. The intra-assay and inter-assay coefficients of variation were 3.8% and 7.2%, respectively. The sensitivity of the assay was 0.3  $\mu\text{g/l}$ .

Serum insulin concentrations were measured with an automated microparticle enzyme immunoassay (MEIA, AxSYM System, Abbott Laboratories, The Netherlands) as described by Rood et al. [11]. The inter-assay coefficient of variation varied between 4.0% and 5.3%. The sensitivity of the assay was 1.0 mU/l.

Serum IGF-1 concentrations were measured by a solid-phase, enzyme-labelled chemiluminescent immunometric assay (Immulite<sup>®</sup> IGF-I, Diagnostic Products Corporation, Los Angeles, USA) in accordance with the manufacturer's instructions. The intra-assay coefficients of variation were 6.1% and 6.4% at IGF-I levels of 49 and 418  $\mu\text{g/l}$ , respectively. The sensitivity of the assay was 20  $\mu\text{g/l}$ .

Serum total thyroxine (total T4) concentrations were measured by a homologous solid-phase, chemiluminescent enzyme immunoassay (Immulite<sup>®</sup> canine total T4, Diagnostic Products Corporation, Los Angeles, USA) in accordance with the manufacturer's instructions. The intra-assay coefficients of variation were 13.8% and 8.2% at total thyroxine levels of 8 and 25 nmol/l, respectively. The sensitivity of the assay was 1.5 nmol/l.

Serum free thyroxine (free T4) concentrations were measured by a competitive analogue immunoassay (Immulite<sup>®</sup> Free T4, Diagnostic Products Corporation, Los Angeles, USA) in accordance with the manufacturer's instructions. The intra-assay coefficients of variation were 7.8% and 5.4% at free thyroxine levels of 8 and 55 pmol/l, respectively. The sensitivity of the assay was 3.9 pmol/l.

Serum thyrotrophin (TSH) concentrations were measured with a homologous solid-phase, two-site chemiluminescent enzyme immunometric assay (Immulite<sup>®</sup> canine TSH, Diagnostic Products Corporation, Los Angeles, USA) in accordance with the manufacturer's instructions. The intra-assay coefficients of variation were 5.0%, 4%, and 3.8% at TSH levels of 0.20, 0.50, and 2.6  $\mu\text{g/l}$ , respectively. The interassay coefficients of variation were 6.3%,

and 8.2% at TSH levels of 0.16 and 2.8  $\mu\text{g/l}$ , respectively. The sensitivity of the assay was 0.03  $\mu\text{g/l}$ .

### 2.3. Diagnostic imaging

With a real-time ultrasound machine equipped with a 6.5–7.5 broadband curved-array transducer (AU5 Epi, Esaote Biomedica, Genova, Italy), the abdomen was examined via the ventral, left, and right approach.

Computed tomography (CT) of the pituitary fossa was performed with the dog under anaesthesia using a sequential mono-slice fourth generation CT scanner (PQS, Picker, Highland Heights, USA). With the dog in sternal recumbency, a series of transverse scans of the skull were made perpendicular to the skull base, from the rostral clinoid processes to the dorsum sellae, using a scanning time of 2 s with 130 kV, 175 mA and 2-mm thick consecutive slices. The scans were obtained both before and following an intravenous bolus of 2 ml/kg of contrast medium (Visipaque 320<sup>®</sup>, iodixanol, containing 320 mg iodixanol/ml, Amersham Health AS, Cork, Ireland).

### 2.4. Histological examination

For histological examination, pituitary tissue, tissue specimens from lung, myocardium, thyroid, and prostate and skin were fixed in 10% neutral buffered formalin and processed for embedding in paraffin. Sections of 4  $\mu\text{m}$  were stained with hematoxylin and eosin (H&E). Immunohistochemical staining on sections of pituitary tissue was performed by the avidin–biotin technique using a polyclonal rabbit antibody to porcine GH, a polyclonal rabbit antibody to human ACTH<sub>1–39</sub>, and a polyclonal rabbit antibody to synthetic  $\alpha$ -MSH (PU060-UP, Biogenex Laboratories, San Ramon, CA, USA).

## 3. Case report

A 10-year-old male uncastrated Dalmatian dog (body weight 30 kg) was referred to the teaching hospital of the Veterinary Clinical Department of the University of Bologna for gait abnormalities consisting of chronic progressive stiffness, difficulty to turn and stand up, and neck rigidity. There was no apparent history of pain. In addition there was polyphagia, weight gain, polyuria and polydipsia (PU/PD), and excessive panting. Over the last 3 years the owner had noticed progressive thickening of the skin and increase in the size of the tongue. The dog had not received any treatment before admission to the hospital.

On physical examination, the dog had an inspiratory stridor. The skin, particularly that of the head and neck, was thick and redundant with many folds. The head and the tongue were markedly enlarged (Fig. 1) and the interdental spaces were widened. The gait was characterized by stiff movements and dragging of the feet.

The only abnormal results on routine laboratory examination were mild anaemia (haematocrit value: 36 l/l; reference range, 37–55 l/l; erythrocytes: 5,360,000/mm<sup>3</sup>; reference range, 5,500,000–8,500,000/mm<sup>3</sup>) and increased concentrations of creatine kinase (CK) (414 U/l; reference range 50–290 U/l), cholesterol (562 mg/dl; reference range, 140–350 mg/dl), and



(a)



(b)

Fig. 1. A male Dalmatian dog at 5 years of age (1a) and at 10 years of age, when acromegaly had developed (1b). Notice the overall increase in body size, redundant skin with many folds on head and neck, and the enlarged tongue.

fructosamine (401  $\mu\text{mol/l}$ ; reference range, 260–370  $\mu\text{mol/l}$ ). Serum concentrations of urea, creatinine, glucose, total protein, albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, bile acids, sodium, potassium, total calcium, and phosphorous were within the respective reference range. The basal and post-ACTH serum cortisol concentrations were 85 nmol/l (reference range 17–132 nmol/l) and 441 nmol/l (reference range 165–480 nmol/l), respectively, consistent with normal adrenocortical function. Urine analysis was unremarkable, except for a low specific gravity (1012) and a slight increase in the urinary total protein/creatinine ratio (0.8; reference range, 0–0.4).

Serum concentrations of total thyroxine (26 nmol/l; reference range 13–51 nmol/l), free thyroxine (29 pmol/l; reference range 11–44 pmol/l), and cTSH (0.29  $\mu\text{g/l}$ ; reference range 0.03–0.38  $\mu\text{g/l}$ ) were all within the respective reference range.

Basal serum GH concentration was markedly elevated (23  $\mu\text{g/l}$ ; reference range 2–5  $\mu\text{g/l}$ ). In addition, the serum IGF-I concentration was clearly elevated (1254  $\mu\text{g/l}$ ; reference range 137–425  $\mu\text{g/l}$ ). The serum GH concentration did not decrease in the glucose tolerance test (Fig. 2) and the somatostatin suppression test (Fig. 3).

Basal serum insulin concentration was high (95 mU/l) and the insulin concentrations became considerably higher after glucose loading (Fig. 2). The serum glucose concentration at 90 min after glucose loading was 210 mg/dl and the glucose disappearance coefficient ( $K$ ) was 1.4 %/min (reference range  $3.9 \pm 0.2$  %/min [4]), indicating that glucose tolerance was impaired despite the elevated serum insulin levels.

Abdominal ultrasonographic findings were unremarkable. Radiographs of the vertebral column showed severe spondylosis deformans extending from the cervical to the lumbosacral spine (Fig. 4). The bone depositions along the ventral margins of the vertebral bodies were fused in the thoraco-lumbar region.

CT scanning of the pituitary area revealed an enlarged pituitary (height 8 mm, reference range <5.4 and pituitary height/brain area ratio 0.5, reference range <0.31). Administration of intravenous contrast medium produced a normal enhancement pattern (precontrast density  $66.2 \pm 8.3$  HU; post contrast density  $103 \pm 9.9$  HU). A small cystic structure with a diameter of about 1.5 mm was present within the pituitary.

The dog was discharged with a presumptive diagnosis of acromegaly due to a GH-secreting pituitary tumour. Therapy was not instituted. Three months later the locomotor problems had become markedly worse and the dog was euthanized at the owner's request. In agreement with the radiographic findings, post-mortem examination revealed multiple fused osteophytes around the ventral portion of the entire vertebral column, which appeared as a single and inflexible structure. The myocardium was pale and leaflets of the mitral valve were thickened (with myxoedematous degeneration). Multiple miliary nodules with a chalky consistency were present in the lungs. The prostate was enlarged. No macroscopic abnormalities were seen in the other organs.

Histological examination of skin specimens revealed moderate epidermal hyperplasia and increased amounts of dermal collagen, resulting in a thickened dermis of dense and compact appearance. Morphometrically [12], the skin specimens were about three times thicker than the skin of healthy Dalmatian dogs. In the myocardium, the amount of fibrous tissue and the number of fat cells were increased, together with scattered myocytolysis. In the prostate there was acinar hyperplasia associated with an increase in amount and density

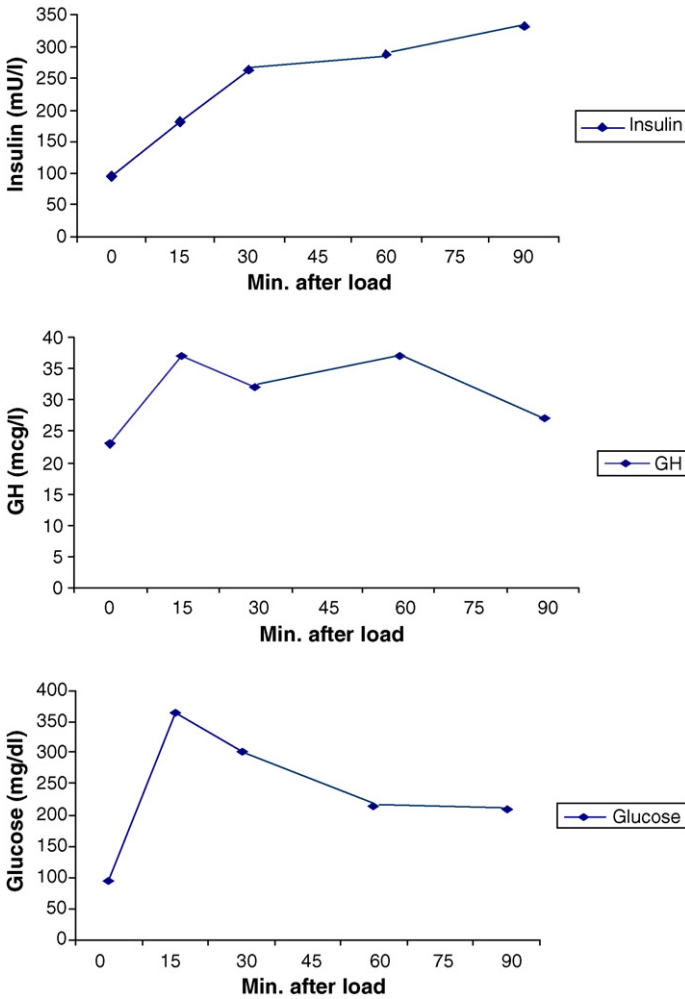


Fig. 2. Serum concentrations of GH, insulin, and glucose at 0, 15, 30, 60, and 90 min after the intravenous administration of 1 g/kg body weight glucose 50% solution in a 10-year-old male Dalmatian dog with acromegaly due to a somatotroph adenoma.

of the interstitial tissue. In the lungs, basophilic areas of calcified granular debris were found scattered throughout the alveolar tissue.

Histological examination of the pituitary gland revealed an acidophilic adenoma. The tumor was well-circumscribed and characterized by broad trabeculae of large polygonal cells separated by thin fibrovascular septa. The cells had hyaline to granular acidophilic cytoplasm and a moderate sized hypochromatic round or indented and sometimes bizarre nucleus. In addition, a small cystic structure was observed in the pars intermedia (Fig. 5). On immunohistochemical investigation the adenoma immunostained positively for GH (Fig. 6), and negatively for  $\alpha$ -MSH and ACTH.

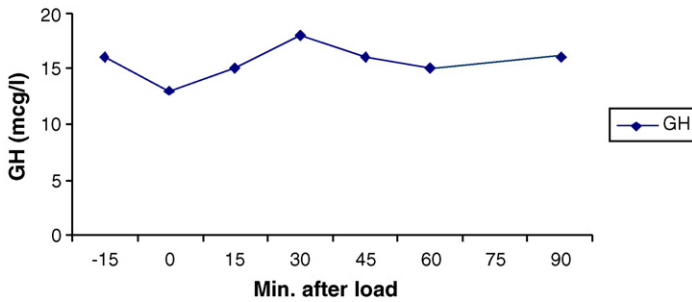


Fig. 3. Serum GH concentrations at –15, 0, 15, 30, 45, 60, and 90 after the intravenous administration of 10  $\mu$ g somatostatin per kg body weight in a 10-year-old male Dalmatian dog with acromegaly due to a somatotroph adenoma.



Fig. 4. Lateral radiograph of the thoracolumbar spine in a 10-year-old male Dalmatian dog with acromegaly due to a somatotroph adenoma. Notice the severe spondylosis on the ventral vertebral bodies due to osteophyte formation.

#### 4. Discussion

The diagnosis of GH excess can generally be established by persistently elevated basal circulating GH concentration [5]. A single high GH concentration may be the result of a secretory pulse in a healthy animal. In the present case, the unaltered serum GH concentrations after somatostatin administration and in the glucose tolerance test pointed to autonomous GH secretion. Moreover, the increased serum IGF-I concentration indicated increased exposure to GH.

In dogs, acromegaly is usually due to progesterone- or progestin-induced GH secretion of mammary origin [3]. As the male dog in the present case report had never been treated with progestins, there had to be another explanation for the cause of acromegaly. In humans and cats, acromegaly is commonly due to excessive secretion of GH by an acidophilic adenoma in the pituitary gland [1,2]. Consequently, pituitary imaging was performed in the present case to investigate whether there was a pituitary tumour. Contrast-enhanced CT indeed revealed that the pituitary was enlarged. Post-mortem examination finally demonstrated an acidophilic pituitary adenoma that stained positively for GH. Although the occurrence of pituitary tumours in dogs which may have had GH excess has been reported before [6–8],



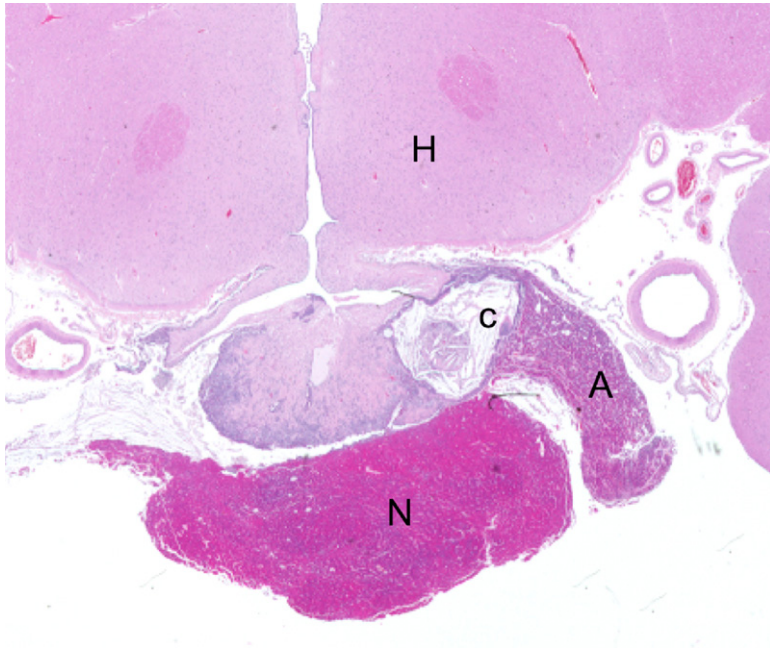


Fig. 5. Hematoxylin–eosin staining of a section from the hypothalamic-pituitary area of a 10-year-old male Dalmatian dog with acromegaly. N indicates an acidophilic adenohypophyseal adenoma. A and H represent the non-tumorous adenohypophysis and the hypothalamus, respectively. A cystic structure (C) was also present.

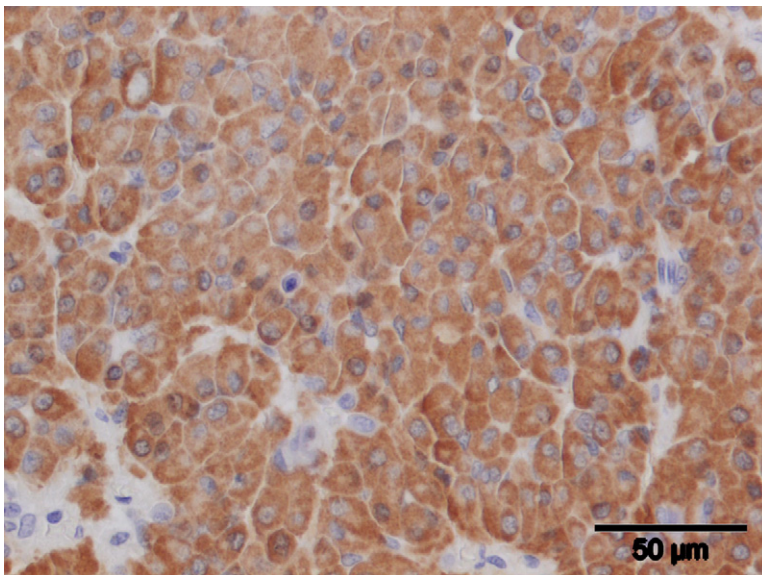


Fig. 6. Immunohistochemical staining of an acidophilic adenoma in a 10-year-old male Dalmatian dog with acromegaly, showing strong and diffuse cytoplasmic immunoreactivity of the adenoma cells to an anti-GH antibody.

to the authors' knowledge this is the first report with definitive prove of GH hypersecretion by a somatotroph adenoma in the dog.

In humans, the earliest signs of acromegaly are coarsening of the facial features and soft tissue swelling of the hands and feet [13,14]. Soft tissue swelling was also an important feature in our dog, which had excessive skin folds particularly around the head and neck. The inspiratory stridor in this dog may have been caused by the increased amounts of soft tissue in the orolingual, oropharyngeal, and orolaryngeal areas [15,16]. Upper-airway narrowing has also been reported in humans and cats with acromegaly, but stridor is not a primary sign in these species [1,17]. Polyphagia, polyuria/polydipsia, excessive painting, macroglossia, and widening of the interdental spaces in the present case were also signs and symptoms characteristic of dogs with acromegaly [5,18,19].

Although the physical signs strongly indicated acromegaly, we performed a complete diagnostic work-up to exclude differential diagnoses. In dogs, primary hypothyroidism is associated with elevated circulating concentrations of GH and IGF-1 [20]. Moreover, physical changes mimicking acromegaly have been reported in dogs with primary hypothyroidism [20]. However, normal circulating concentrations of free T<sub>4</sub>, total T<sub>4</sub>, and cTSH excluded primary hypothyroidism in the present case.

The only abnormal findings on routine blood examination were mild anemia and an elevated serum fructosamine concentration. A dose-related normochronic, normocytic, non-regenerative anemia has been reported in dogs treated with pharmacological doses of porcine GH [21].

The most common recognized manifestation of acromegaly in cats is insulin-resistant diabetes mellitus [1]. In humans, hypersecretion of GH induces insulin resistance and glucose intolerance in 29–45% of acromegalic patients and overt diabetes mellitus in 10–20% [14]. GH-induced insulin resistance appears to be due to postreceptor impairment of the action of insulin [22]. GH is also known to be a powerful diabetogenic agent in the dog [23]. In our dog, basal glucose concentration was within the reference range at the time of diagnosis and 3 months later, and glucosuria was not found. However, the increased serum fructosamine concentration pointed to periods of hyperglycemia, e.g. after meals. This explanation is supported by the observation that the dog was still hyperglycaemic at 90 min after glucose administration in the glucose tolerance test. Moreover, the markedly elevated plasma insulin concentrations were consistent with severe insulin resistance. Therefore, it may be concluded that our dog was in a pre-diabetic state.

The main reasons for referral of our dog were gait abnormalities consisting of chronic progressive stiffness, difficulty to turn and stand up, and neck rigidity. These abnormalities were due to severe spondylosis deformans of the entire vertebral column and maybe also to similar osteophyte formation in other joints. Osteophyte formation has also been reported in humans, rats and cats with acromegaly [24,25]. The presence of multiple osteophytes may be ascribed to an IGF-1 mediated growth-promoting action on bone [26]. Based on experimental evidence, the following pathophysiological sequence of events has been suggested [24]. GH stimulates local production of IGF-1 in cartilage which, combined with increased levels of circulating IGF-1, results in hyperfunction of chondrocytes and increased matrix synthesis. In addition, regenerative fibrocartilage proliferates disproportionately, presumably as a result of GH stimulation. The regenerative fibrocartilage subsequently becomes calcified, resulting in osteophyte formation.

The cutaneous changes in the present case, with dermal hyperplasia as the most striking feature, have been reported previously in canine acromegaly [27]. In addition to epidermal hyperplasia and an increased amount of dermal collagen, the thick skin folds in acromegaly have been ascribed to mucopolysaccharide accumulation [28].

On CT scanning the pituitary gland was judged enlarged based on both the height of the pituitary and the pituitary height/brain area ratio in comparison with reference values [29]. Diagnostic imaging of the pituitary also revealed the presence of a cystic structure. Histological examination showed that the cystic structure was located outside the acidophilic adenoma and thus was most likely an incidental finding. Moreover, pituitary cysts are relatively common in dogs [30].

In conclusion, our Dalmatian dog with acromegaly and insulin resistance is the first case report with proven hypersecretion of GH by a somatotroph adenoma.

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## References

- [1] Peterson ME, Taylor RS, Greco DS, Nelson RW, Randolph JF, Foodman MS, et al. Acromegaly in 14 cats. *J Vet Intern Med* 1990;4:192–201.
- [2] Rijnberk A, Kooistra HS, Mol JA. Endocrine diseases in dogs and cats: similarities and differences with endocrine diseases in humans. *GH IGF Res* 2003;13:158–64.
- [3] Selman PJ, Mol JA, Rutteman GR, Garderen Evan, Rijnberk A. Progesterin-induced growth hormone excess in the dog originates in the mammary gland. *Endocrinology* 1994;134:287–92.
- [4] Eigenmann JE, Eigenmann RY, Rijnberk A, van der Gaag I, Zapf J, Froesch ER. Progesterone-controlled growth hormone overproduction and naturally occurring canine diabetes and acromegaly. *Acta Endocrinol* 1983;104:167–76.
- [5] Kooistra HS. Acromegaly and pituitary dwarfism. In: Ettinger SJ, Feldman EC, editors. *Textbook of Veterinary Internal Medicine*. 6th ed. Philadelphia, PA: WB Saunders; 2005. p. 1498–502.
- [6] Lucksch F. Über Hypophysentumoren beim Hunde. *Tierärztl Arch* 1923;3:1–16.
- [7] King JM, Kavanaugh JF, Bentinck-Smith J. Diabetes mellitus with pituitary neoplasms in a horse and in a dog. *Cornell Vet* 1962;52:133–45.
- [8] van Keulen LJM, Wesdorp JL, Kooistra HS. Diabetes mellitus in a dog with a growth hormone-producing acidophilic adenoma of the adenohypophysis. *Vet Pathol* 1996;33:451–3.
- [9] Lundbäck K. Intravenous glucose tolerance as a tool in definition and diagnosis of diabetes mellitus. *Br Med J* 1962;1:1507–13.
- [10] Eigenmann JE, Eigenmann RY. Radioimmunoassay of canine growth hormone. *Acta Endocrinol* 1981;98:514–20.
- [11] Rood JC, Lovejoy JC, Tulley RT. Comparison of a radioimmunoassay with a microparticle enzyme immunoassay of insulin for use with the minimal model method of determining whole-body insulin sensitivity. *Diabetes Technol Ther* 1999;1:463–8.
- [12] Diana A, Preziosi R, Guglielmini C, Degliesposti P, Pietra M, Cipone M. High-frequency ultrasonography of the skin of clinically normal dogs. *Am J Vet Res* 2004;65:1625–30.
- [13] Gordon DA, Hill FM, Ezrin C. Acromegaly: a review of 100 cases. *Can Med Assoc J* 1962;87:1109–60.
- [14] Jadresic A, Banks LM, Child DF, Diamant L, Doyle FH, Fraser TR, et al. The acromegaly syndrome. Relation between clinical features, growth hormone values and radiological characteristics of the pituitary tumours. *QJ Med* 1982;51:189–204.

- [15] Eigenmann JE, Venker-van Haagen AJ. Progestagen-induced and spontaneous canine acromegaly due to reversible growth hormone overproduction: clinical picture and pathogenesis. *J Am Anim Hosp Assoc* 1981;17:813–22.
- [16] Rijnberk A. Hypothalamus-pituitary system. In: Rijnberk A, editor. *Clinical endocrinology of dogs and cats*. Dordrecht, The Netherlands: Kluwer Academic Publishers; 1996. p. 11–34.
- [17] Morewood DJ, Belchetz PE, Evans CC, Whitehouse GH. The extrathoracic airway in acromegaly. *Clin Radiol* 1986;37:243–6.
- [18] Concannon P, Altszuler N, Hampshire J, Butler WR, Hansel W. Growth hormone prolactin and cortisol in dogs developing mammary nodules and an acromegaly-like appearance during treatment with medroxyprogesterone acetate. *Endocrinology* 1980;106:1173–7.
- [19] Rijnberk A, Eigenmann JE, Belshaw BE, Hampshire J, Altszuler N. Acromegaly associated with transient overproduction of growth hormone in a dog. *J Am Vet Med Assoc* 1980;177:534–7.
- [20] Lee WM, Diaz-Espineira M, Mol JA, Rijnberk A, Kooistra HS. Primary hypothyroidism in dogs is associated with elevated growth hormone release. *J Endocrinol* 2001;168:59–66.
- [21] Prahalada S, Stabinski LG, Chen HY, Morrissey RE, De Burchett G, Holder D, et al. Pharmacological and toxicological effects of chronic porcine growth hormone administration in dogs. *Toxicol Pathol* 1998;26:185–200.
- [22] Bratusch-Marrain PR, Smith D, DeFronzo RA. The effect of growth hormone on glucose metabolism and insulin secretion in man. *J Clin Endocrinol Metab* 1982;55:973–82.
- [23] Eigenmann JE, Eigenmann RY. Influence of medroxyprogesterone acetate (Provera) on plasma growth hormone levels and on carbohydrate metabolism. II. Studies in the ovariectomized, oestradiol-primed bitch. *Acta Endocrinol (Copenh)* 1981;98:603–8.
- [24] Colao A, Ferone D, Marzullo P, Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endocr Rev* 2004;25:102–52.
- [25] Peterson ME, Randolph JF, Mooney CT. In: Sherding RG, editor. *Endocrine diseases*. Philadelphia: WB Saunders Co.; 1994. p. 1403–506.
- [26] Okazaki K, Jingushi S, Ikenoue T, Urabe K, Sakai H, Ohtsuru A, et al. Expression of insulin-like growth factor I messenger ribonucleic acid in developing osteophytes in murine experimental osteoarthritis and in rats inoculated with growth hormone-secreting tumor. *Endocrinology* 1999;140:4821–30.
- [27] Scott DW, Concannon PW. Gross and microscopic changes in the skin of dogs with progestagen-induced acromegaly and elevated growth hormone levels. *J Am Anim Hosp Assoc* 1982;19:523–7.
- [28] Matsuoka LY, Wortsman J, Kupchella CE, Eng A, Dietrich JE. Histochemical characterization of the cutaneous involvement of acromegaly. *Arch Intern Med* 1982;142:1820–3.
- [29] Kooistra HS, Voorhout G, Mol JA, Rijnberk A. Correlation between impairment of glucocorticoid feedback and the size of the pituitary gland in dogs with pituitary-dependent hyperadrenocorticism. *J Endocrinol* 1997;152:387–94.
- [30] Rao RR, Bhat NG. Incidence of cysts in pars distalis of mongrel dogs. *Indian Vet J* 1971;48:128–35.