ADENOCARCINOMA OF THE ADRENAL GLAND IN A FEMALE DOG

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ABSTRACT

The aim of this article is to describe a case of adrenocortical neoplasm with manifestation of hyperadrenocorticism. Adrenocortical tumors originate from different types of cells and present varied clinical manifestations, which can be functional or non-functional. Adenocarcinomas are autonomous and functional in most cases, leading to excessive secretion of glucocorticoids, regardless of pituitary control. They corroborate the occurrence of hyperadrenocorticism (HAC) due to interference in the synthesis of cortisol. Clinical signs can be observed, as polyuria, compensatory polydipsia, polyphagia, blood pressure alterations, cardiac, renal and endocrine dysfunctions, among others. Diagnosis can be made in various ways, such as urinary cortisol measurements, adrenocorticotropic hormone stimulation, low-dose dexamethasone suppression tests, and imaging tests and histopathology. This article reports the case of a 13-year-old mixed-breed female dog with signs of polyuria and polydpsia. After discarding the initial diagnoses (diabetes mellitus and/or renal alterations), HAC was suspected, with further tests being performed. The test results showed an increase in the adrenal region, and adrenalectomy and hormone replacement with trilostane were recommended. The diagnosis of HAC was confirmed by histopathology as HAC secondary to adrenal gland adenocarcinoma. The patient also developed diabetes mellitus during postoperative treatment with prednisone, which made it necessary to discontinue the medication.

Keywords: adrenocortical tumors, endocrine disease, hyperadrenocorticism

ADENOCARCINOMA DA GLÂNDULA ADRENAL EM UMA CADELA

RESUMO

O objetivo deste artigo é descrever um caso de neoplasia adrenocortical com manifestação de hiperadrenocorticismo. Tumores adrenocorticais são originados de diversos tipos de células e apresentam manifestação clínica variada, podendo ser funcionais ou não funcionais. Os adenocarcinomas são autônomos e funcionas na maioria dos casos, levando a secreção excessiva de glicocorticóides, independente do controle da hipófise. Eles corroboram com a ocorrência de hiperadrenocorticismo (HAC) por interferência na síntese de cortisol. Os sinais clínicos observados podem ser poliúria, polidipsia compensatória, polifagia, alterações pressóricas, disfunções cardíacas, renais e endócrinas, entre outros. Estas manifestações clínicas podem se apresentar de forma isolada ou associada. O diagnóstico pode ser obtido de diversas formas, como dosagens de cortisol urinário, estimulação de hormônio adrenocorticotrópico, testes de supressão com baixa dose de dexametasona e por testes de imagem. No entanto, o diagnóstico definitivo baseia-se no uso da histopatologia. Este artigo

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relata o caso de uma fêmea sem raça definida, de 13 anos de idade, com sinais de poliúria e polidpsia. Após o descarte dos diagnósticos iniciais (diabetes mellitus e/ou alterações renais), suspeitou-se de HAC, com a realização de novos exames. Os resultados dos exames evidenciaram aumento da região adrenal, sendo recomendada a adrenalectomia e reposição hormonal com trilostano. O diagnóstico de HAC foi confirmado pela histopatologia como sendo HAC secundário a adenocarcinoma de glândula adrenal. A paciente desenvolveu ainda um quadro de diabetes mellitus durante o tratamento com prednisona no pós-operatório, sendo necessário interromper a medicação.

Palavras-chave: tumores adrenocorticais, doença endócrina, hiperadrenocorticismo

ADENOCARCINOMA DE LA GLÁNDULA SUPRARRENAL EN UNA PERRA

RESUMÉN

El objetivo de este artículo es describir un caso de neoplasia adrenocortical con manifestación de hiperadrenocorticismo. Los tumores adrenocorticales se originan a partir de diferentes tipos de células y presentan una variada manifestación clínica, que puede ser funcionante o no funcionante. Los adenocarcinomas son autónomos y funcionales en la mayoría de los casos, lo que lleva a una secreción excesiva de glucocorticoides, independientemente del control pituitario. Corroboran la aparición de hiperadrenocorticismo (HAC) al interferir con la síntesis de cortisol. Los signos clínicos observados pueden ser poliuria, polidipsia compensatoria, polifagia, alteraciones de la presión arterial, disfunciones cardíacas, renales y endocrinas, entre otras. Estas manifestaciones clínicas pueden presentarse de forma aislada o en asociación. El diagnóstico se puede obtener de varias maneras, como mediciones de cortisol urinario, estimulación con hormona adrenocorticotrópica, pruebas de supresión con dosis bajas de dexametasona y pruebas de imagen. Sin embargo, el diagnóstico definitivo se basa en el uso de la histopatología. Este artículo reporta el caso de una perra mestiza de 13 años con signos de poliuria y polidipsia. Tras descartar los diagnósticos iniciales (diabetes mellitus y/o alteraciones renales), se sospechó HAC, realizándose nuevas pruebas. Los resultados de los exámenes mostraron un aumento en la región suprarrenal, por lo que se recomendó adrenalectomía y reemplazo hormonal con trilostano. El diagnóstico de CAH se confirmó por histopatología como CAH secundaria a adenocarcinoma de la glándula suprarrenal. La paciente también desarrolló diabetes mellitus durante el tratamiento con prednisona en el postoperatorio, siendo necesario suspender la medicación.

Palabras clave: tumores adrenocorticales, enfermedad endocrina, hiperadrenocorticismo

INTRODUCTION

Adrenocortical tumors are originated from several cells and present varied clinical manifestations, which may or may not be functional. Generally, adenocarcinomas are autonomous and functional, inducing excessive secretions of glucocorticoids, which are independent of pituitary control (HAC) (1). Primary canine adrenal tumors, adenomas and adenocarcinomas, represent 44.1% and 11.7% of neoplasms of the adrenal gland, respectively (2). Eventually, 90% of dogs with functional adrenocortical tumor HAC tend to be elderly and females are affected 60-65% of cases (3). The actions of cortisol leads to clinical signs. The symptoms presented, isolated or associated, are polyuria (80%), polydipsia (82.6%), polyphagia (86.1%), systemic hypertension – SH (59-86% of the cases of HAC), congestive heart failure - CHF, kidney disease, *diabetes mellitus* - DM (on average 16% of cases),

alopecia without itchiness, among others (3-5). Besides the expected abnormalities, there are changes in leukogram, cholesterol, triglycerides and glucose.

In addition to these, a slight increase in bile acids, increased serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP) (5). For the screening of adrenal adenocarcinoma, laboratory tests such as measurement of urinary cortisol, adrenocorticotropic hormone - ACTH stimulation, low-dose dexamethasone suppression test (LDDST) and imaging tests (1) were performed, and definitive diagnosis is confirmed by histopathology. Treatment for functional tumors including mitotane or trilostane, and / or excisions (5). Correlating the findings and clinical conduct with data from the literature, the objective of the present study is to report the clinical and surgical condition of a dog with adrenal adenocarcinoma.

CASE REPORT

A mixed breed female dog, 13 years old, 17 kg, with signs of polydipsia and polyuria was taken at a veterinary clinic in the city of Belo Horizonte/MG, Brazil. On clinical examination, the mucous membranes and body temperature were normal and the measured systolic blood pressure (SBP) was 170 mmHg. Tests were made to rule out suspicions of DM and kidney disease. Serological tests, ELISA and indirect immunofluorescence - total dilution (IIF), were performed for canine visceral leishmaniasis, which presented a "non-reactive" result. Laboratory tests such as biochemical tests and uroanalysis were performed (Table 1). On abdominal ultrasound (US), the left kidney measured 5.03 cm, with the usual topography and morphology, in addition to a preserved echogenic structure; the right kidney was 5.06 cm, with loss of cortico-medullary relation / definition, with diverticular calcinosis and regular borders. The left adrenal showed altered morphology, heterogeneous parenchyma with a significant increase in volume of caudal pole (2.80 x 2.93 cm). The gallbladder with anechoic content, normal thick wall, discreet bile mud and regular edges. In addition, splenomegaly and heterogeneous splenic parenchyma with diffuse anechoic structures.

Table 1. Description of the laboratory tests performed and their respective results.

***Laboratory tests performed**		
Biochemical tests	**Results (mg/dL)**	**Canine Reference Values (mg/dL)**
Triglycerides	247.0	20.00 - 112.00
Total Cholesterol	241.0	125.0 - 270.0
HDL	185.80	60.0 - 140.0
LDL	5.80	34.0 - 115.0
VLDL	49.40	up to 25.0
Glucose	104.0	65 - 118
Uroanalysis		
Urinary protein	27.00 mg/dL	
Creatinine	15.23 mg/dL	> 1 year: 0.5 a 1.60
Urine protein to creatinine ratio- UP/C	1.772	< 1.0

† Consider: mg/dL - milligrams per deciliter.

In view of the suspicion of HAC, the LDDST test was performed by radioimmunoassay, with collection time at 11:00 AM and 7:00 PM (first and second dosages respectively). New laboratory tests was performed and the values of total proteins, albumin, globulin showed no discrepancies in relation to the reference value (Table 2). Chest radiography did not show the presence of nodules. The echocardiogram showed mild atrioventricular and moderate aortic valve insufficiency in addition to overload signs of the right chambers. Left ventricular (LV) systolic function was preserved, although there were signs of diastolic dysfunction. On

tomography: liver with slightly increased dimensions, presence of 3 lymph nodes, possible hepatic origin, with volumetric increase (slight); splenic parenchyma full of multiple isodense and hypercaptant nodular areas (<1.0 cm). Topical kidneys, with absence of pyelocalyal dilation, left adrenal with moderate / intense increase, irregular but defined contours, and uptake of heterogeneous contrast (6.5 cm x 4.1 cm x 4.2 cm) without invasion of the vena cava. Right adrenal preserved. There has been previous therapy with trilostane (1 mg / kg / BID). After clinical improvement, the animal underwent left adrenalectomy and splenectomy. Histopathologically, it was noticed adrenocortical carcinoma with fibrous capsular invasion and margin involvement. In the post-surgical period, the cortisol level was restored with prednisone replacement (initial dose 0.5 mg / kg / BID for 48 hours). This was followed by the gradual weaning from corticotherapy starting (0.25 mg / kg / BID for 21 days) and then 0.25 mg / kg / SID for 3 weeks, before the end of the protocol due to the development of DM.

Table 2. Description of the laboratory tests performed and their respective results.

***Laboratory tests performed**				
Low-dose dexamethasone suppression test	**First dosage (11 AM)**		**Second dosage (9 PM)**	
	53.10 ng/ml		36.60 ng/ml	
Erythrogram	**Results**		**Canine Reference Values**	
Erythrocytes	7.32 M/µL		5.50 – 8.50 M/µL	
Hemoglobin	16.6 g/dL		12.0 - 18.0 g/dL	
Hematocrit	49.9 %		37.0 – 55.0 %	
MCV	68.2 fl		60.0 – 77.0 fl	
MCH	22.7 pg		19.5 – 24.5 pg	
MCHC	33.2 /dL		32.0 – 36.0 /dL	
Platelets	406.000 /µL		150.000 - 500.000 /µL	
Leukogram				
Leukocytes - Global	14.500/µL		6.000 - 17.000/mm3	
	(%)	(/µL)	(%)	(/µL)
Segmented Neutrophils	88	12.760	60 -77	3.000 - 11.500
Lymphocytes	6	870	12 - 30	1.200 - 4.800
Monocytes	2	290	3 - 10	150 - 1.350
Eosinophils	4	580	2 - 10	100 - 1.250
Basophiles	0	0	Rare	Rare
Metamyelocytes	0	0	0 - 1	0
Myelocytes	0	0	0	0
Blasts	0		0	0
Serum Biochemistry				
Creatinine	1.05 mg/dL		0.60 - 1.60 mg/dL	
Alkaline phosphatase	185 U/L		0 - 93 U/L	
Glutamyl transferase	12 U/L		0.0 - 10.0 U/L	
Urea	39 mg/dL		21 - 60 mg/dL	
Total Proteins	6.50 g/dL		5.40 - 7.70 g/dL	
Albumin	2.87 g/dL		2.30 - 3.80 g/dL	
Globulins	3.63 g/dL		2.30 - 5.20 g/dL	
UP/C	0.79			
Pyruvic Transaminase	114 UI/L		0 – 102 UI/L	

† **Consider:** ng/mL - nanograms per milliliter; fl – femtoliters; pg- picograms; dL – deciliter; µL – microliters; M/µL - million per microliter; mm^3 - microliter of blood mg/dL - milligrams per deciliter; g/mL - grams per deciliter; U/L - atomic mass unit per liter; UI/L - international units per liter; MCV - Mean Corpuscular Volume; MCH - Mean Corpuscular Hemoglobin; MCHC - Mean corpuscular hemoglobin concentration; UP/C - Urine protein to creatinine ratio

RESULTS AND DISCUSSION

The clinical signs of polydipsia, polyuria and >SBP presented, made possible the suspicion of DM and kidney disease. Laboratory results did not confirm the suspicion, due to the usual glucose concentration (104 mg / dL). The change in triglycerides, total cholesterol, HDL and VLDL alarmed HAC. The US revealed a left adrenal volumetric increase with heterogeneous parenchyma, suggesting tumoral HAC. Under these conditions, excessive glucocorticoid secretion and the appearance of the clinical signs observed above occur. These are in accordance with the literature that reports adrenal functional adenocarcinoma as responsible for excessive secretion without pituitary control (3). HAC hinders the release of vasopressin, increasing the glomerular filtration rate and limiting water reabsorption in the collecting ducts. Urine is diluted with a density <1.020 in 85% of cases (6). SH is detected in >60% of those affected, and concentric LV hypertrophy may occur. Pressure elevation occurs secondarily to chronic HAC due to catecholamines; higher renin secretions; reductions in vasodilating prostaglandins and secretive increases in mineralocorticoids (1,6).

In the CBC, only neutrophilia and lymphopenia were observed. In the typical pattern of HAC, there may be mild erythrocytosis, leukogram of stress and thrombocytosis. The increase in serum glucocorticoids induces the release of mature neutrophils into the circulation and a decrease in the tissue. Eosinopenia comes from decreased spinal cord release and increased sequestration / apoptosis. The lymphopenia of the circulating lymphocyte redistribution to the spinal cord (1). Abnormalities can be found such as hypercholesterolemia, hypertriglyceridemia, lipemia, hyperglycemia, hypostenuria / isostenuria, glycosuria, proteinuria, cystitis, slight increases in bile acids (pre / postprandial), increased serum ALT and increased ALP (5). Increases of this originate from the specific hepatic isoenzyme production, induced by glucocorticoids, with increments of> 5-40 times, being more sensitive to HAC (1,3). The patient above presented proteinuria (UP/C 1,772) and ALP with a slight increase, which does not exclude the diagnosis of HAC (3). ALT increases result from hepatocellular damage from steatosis and glycogen accumulation (1).

LDDST has high sensitivity (85-100%) and accuracy (95%) for canine HAC. LDDST generates sufficient negative feedback in healthy dogs, suppressing the secretion of pituitary ACTH, and reducing plasma cortisolic concentration (24-48 h). Cortisol was measured before and 8h after intravenous application of dexamethasone (0.01 mg / kg). Plasma cortisol levels in dogs with an adrenocortical tumor do not decrease below the benchmark predetermined by laboratories (14.00 ng / mL) (1). In this report, baseline cortisol confirmed the suspicion of post-suppression HAC due to the first dosage (53.10 ng / mL) and the second (36.70 ng / mL). Organic changes in the US were important to diagnose HAC, being a more sensitive test to detect recurrences and metastases than hormonal analyzes. Adrenal adenocarcinoma is usually a larger size, with irregular margins, local and vascular invasion (1). Trilostane is well tolerated by dogs (<incidence of side effects) and is the first choice for ACTH-dependent HAC. It competitively inhibits the steroidogenic enzyme 3-beta-hydroxysteroid dehydrogenase, which intermediates the conversion of pregnelone - progesterone (precursors of cortisol), with a cortisolic suppressant effect. The recommended dose is 2-6 mg / kg every 24 h (7). The animal improved after starting trilostane (1 mg / kg / BID) with a decrease in the reported symptoms.

For treatment, clinical and surgical options should be analyzed with caution. Adrenal tumor HAC has a better prognosis after excisions. In this study, after left adrenalectomy, the serum cortisol level was restored after using prednisone (0.5 mg / kg / BID for 48 hours), considering pharmacological weaning. The dose was readjusted to 0.25 mg / kg / BID for 3 weeks and then to the SID interval. Splenic histopathology revealed an epithelioid

macrophage inflammatory infiltrate in nodular areas, contesting the metastatic hypothesis. The adrenal showed neoplastic proliferation with expansive and infiltrative growth. Adrenalectomies, in the absence of metastases, provide better expectations than pituitary HAC, with no indications of a chemotherapeutic protocol after surgical procedure. About 16% of patients with HAC develop DM with related signs (4,5). Drug with drawal before the end of therapy was necessary due to DM. Tumors at the adrenal level can systematically alter the affected animals. Thus, the present report described the case of a female dog with HAC secondary to adrenal adenocarcinoma with determination based on an association of diagnostic tools. The use of trilostane promoted clinical improvement to the animal after clinical indication, followed later by adrenal excision. However, it was necessary to use corticotherapy in the postoperative period, although this was interrupted by the development of DM.

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