Pathological Findings in the Adrenal Glands of 80 Dogs

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ABSTRACT

Background: The adrenal glands development important endocrine functions and can be affected by primary or secondary diseases. These adrenal gland pathologies may induce clinical syndromes resulting from abnormalities in the production and secretion of hormones. Data about pathological changes in dogs are scarce. Therefore, the aim of the present study was to identify and evaluate the histopathological and epidemiological features of adrenal changes in dogs submitted to necropsy examination from 2005 to 2016 in a Veterinary Teaching Hospital, Londrina, Paraná, Brazil.

Material, Methods & Results: During this period, 80 animals presented alterations of adrenal gland, representing 5.5% of all necropsied dogs. The pure breed dogs representing 58.6% and mixed breed 41.4%; 53.4% were female and 46.6% were male. The non-neoplastic adrenal lesions were more frequently (57.5%) compared to the neoplastic changes (42.5%). Most of the adrenal glands lesions occurred in older dogs (60%), following by the middle aged (31.25%) and young dogs (8.75%). The main non-neoplastic lesions observed in the adrenal glands were of hyperplastic (69.5%) and circulatory (26%) origin, among the earlier, 68.8% were diffuse hyperplasia and 31.2% nodular hyperplasia. The nodular hyperplasia was classified as micronodular multifocal in 40% of the glands with nodular hyperplasia, macronodular multifocal in 30%, micronodular diffuse in 20%, and micronodular focal in 10%. The neoplasms observed were adrenocortical adenoma (ACA) in 44.1%, pheochromocytomas in 23.5% and adrenocortical carcinomas (ACC) in 11.7% of the dogs with adrenal tumors. Metastasis from other primary tumors were observed in 20.6%.

Discussion: The data in veterinary literature about the frequency of changes in adrenal gland of dogs are scarce and focus features of diagnosis by ultrasound examination. Most of the adrenal changes observed in the present study were incidental findings observed during the necropsy examination and no specific clinical signs were observed. Non-neoplastic adrenal lesions, mainly of hyperplastic origin, were more frequently observed compared to the neoplastic changes. Differing from previous studies, the diffuse hyperplasia was the most common non neoplastic finding in the adrenal glands. Considering the subclassification of nodular hyperplasia, the multifocal micronodular and macronodular multifocal pattern were the most frequent. In veterinary literature, there are no data about frequency of nodular hyperplastic subtypes. However, in humans the subclassification of nodular hyperplasia is associated to development of endocrine disorders. Previous studies reported lower incidence of neoplastic changes in adrenal gland of dogs compared to the present results. The adrenocortical adenoma was the most common primary tumor, followed by the adrenocortical carcinoma, pheochromocytoma and adrenocortical carcinoma. Congestion and hemorrhage were common findings observed in the adrenal gland primary tumors. On the other hand, necrosis and inflammatory infiltrate were observed only in the adrenocortical carcinomas. These histopathological features may be used as tool in the differential diagnosis between well differentiated adrenocortical carcinoma and adenoma. The histopathological examination was fundamental to differential and definitive diagnosis of all canine adrenal gland disorders observed.

Keywords: adrenal gland, histopathological findings, dogs.
Descritores: adrenal, achados histopatológicos, cão.

INTRODUCTION

The adrenal glands can be affected by diseases associated with circulatory, inflammatory, hyperplastic, and neoplastic (primary or metastatic) processes [21], and may induce clinical syndromes resulting from abnormalities in the production and secretion of hormones [18].

Most dogs with functional adrenocortical alterations present typical clinical signs of excess glucocorticoid, with polyuria and polyphagia as the dominating features. Other signs of Cushing`s syndrome of dogs include abdominal obesity, weight gain, fatigue, muscle atrophy, cutaneous lesions [2], and are similar to those reported in humans [8]. Dogs with functional pheochromocytomas can present cardiomyopathy and systemic hypertension due the norepinephrine secretion [9].

Previous studies have evaluated the clinical, imaging features and therapy of dogs with hyperadrenocorticism due to adrenocortical tumors [3,13,23,26,29], and cardiomyopathies associated with pheochromocytomas [9]. However, data about frequency and incidence of adrenal gland changes in dogs are scarce [15,25,28]. The aim of this study was characterize the pathological findings of adrenal changes in dogs submitted to necropsy examination in a Veterinary Teaching Hospital from 2005 to 2015.

MATERIALS AND METHODS

Local

A retrospective survey of all adrenal glands submitted for histopathological diagnosis from dogs necropsied at the Laboratory of Animal Pathology, Universidade Estadual de Londrina, Brazil from January 2005 to December 2016 was done.

Data

Data relative to breed, age, sex, clinical signs and histopathological diagnoses of all dogs with an adrenal-associated disease were reviewed and tabulated. When necessary, formalin-fixed and paraffin-embedded block were sectioned at sections of 4μm and stained with hematoxylin-eosin (H&E) for histopathological evaluation. Hyperplastic adrenocortical lesions were classified as: diffuse (diffuse hyperplastic proliferation without nodules formation), micronodular (nodules measuring less than 0.5 cm in diameter), and macronodular (nodules measuring more than 0.5 cm in diameter) with focal, multifocal or diffuse localization [8].

RESULTS

During the evaluated period of 11 years, 80 animals presented alterations to the adrenal gland, representing 5.5% (80/1454) of all necropsied dogs. The pure breed dogs representing 58.6% (852/1454) and the mixed breed dogs 41.4% (602/1454). The sexual distribution of the necropsied dogs was 53.4% female (776/1454) and 46.6% male (678/1454). Total of 100 adrenal glands were submitted to histopathological evaluation since 20 dogs (25%) showed bilateral lesions.

The frequency, percentage, age and sex distribution of the non-neoplastic and neoplastic adrenal disorders are presented in Table 1. Non-neoplastic adrenal lesions were more frequently (57.5%; 46/80) and the neoplastic changes were observed in 42.5% (34/80). Most of the adrenal glands lesions occurred in older dogs (11 years or more), representing 60% (48/80), following by middle aged (6 to 10 years) 31,25% (25/80) and young dogs (until five years) 8.75% (7/80). Females represented 75% (60/80) of the dogs with adrenal pathological changes.

Pure breed dogs represented 58.8% (47/80) of the animals evaluated during the period and mixed breeds 41.2% (33/80). The most affected breeds were Poodle 18.1% (6/47), Rottweiler 18.1% (6/47), German Shepherd 12.1% (4/47), Boxer 9% (3/47) and Yorkshire 9% (3/47). The reported clinical signs were nonspecific (anorexia, weakness, and tachypnea) in most dogs (73/80) with any adrenal disorder. However, clinical signs of hyperadrenocorticism as polydipsia, polyuria, symmetrical alopecia and abdominal distension were observed in 6.2% (5/80) being associated with ACA (2), diffuse hyperplasia (2) and nodular hyperplasia (1); while only one dog with adrenal atrophy (1.25%, 1/80) had clinical signs of hypoadrenocorticism. Clinical signs of tachypnea and tachycardia associate do excess of catecholamine production were observed in one dog with pheochromocytoma (1.25%, 1/80).

The most of the adrenal changes developed in the cortical region (Figure 1). The main non-neoplastic lesions observed in the adrenal glands were of hyperplastic 69.5% (32/46) and circulatory 26% (12/46) origin, among the earlier, 47.8% were diffuse hyperplasia (22/46) and 32.6% nodular hyperplasia (15/46). Further, nodular hyperplasia was observed as a micronodular multifocal pattern in 40% (5/10) of the glands, macronodular multifocal in 30% (3/10), micronodular diffuse in 20% (2/10), and micronodular focal in 10% (1/10). The mean age of the dogs with non-neoplastic adrenal lesions was 9.3 years; female (36/46) dogs were over represented.

Table 1. Frequency of non-neoplastic and neoplastic histological alterations associated with the mean age and sex of 80 dogs.

| Diagnosis	Frequency of alterations	% of the total adrenal lesions	Mean age (years)	Sex M	Sex F
Non-neoplastic	(%/total non-neoplastic lesions)				
Atrophy	1 (2.2%)	1.2%	2 (2)	0	1
Congestion	4 (8.6%)	5%	11 (7 to 14)	2	2
Diffuse hyperplasia	22 (47.8%)	27.5%	9.5 (2 to 19)	5	17
Hemorrhage	8 (17.4%)	10%	7.5 (1 to 14)	2	6
Lymphocytic infiltrate	1 (2.2%)	1.2%	6 (6)	0	1
Nodular hyperplasia	10 (21.8%)	12.5%	10.6 (7 to13)	1	9
Total	46 (100%)	57.5 %	9.3 (2 to19)	10	36
Neoplastic	(%/total neoplastic lesions)				
Adrenocortical adenoma	15 (44.1%)	18.7%	11.6 (7to15)	4	11
Adrenocortical carcinoma	4 (11.8%)	5%	12.6 (9to16)	0	4
Metastasis	7 (20.6%)	10%	9 (8-10)	1	6
Pheochromocytoma	8 (23.5%)	8.8%	9.2 (6 to 11)	5	3
Total	34 (100%)	42.5%	10.6 (6 to 16)	10	24
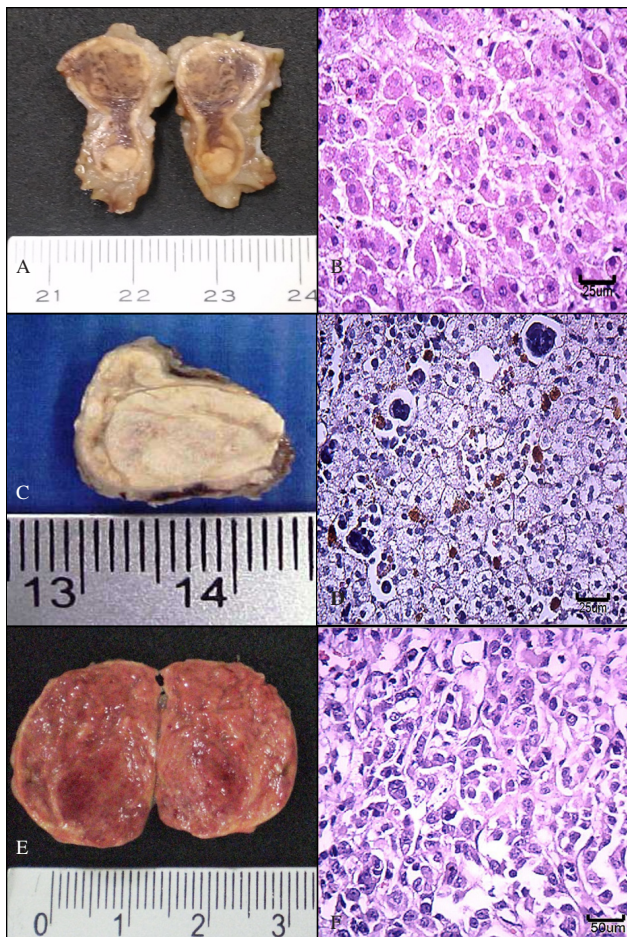
Figure 1. Adrenocortical disorders in dogs. A- Focal micronodular hyperplasia- nodule well delimitated, yellowish and firm in cortical region (blue arrow). B- Microscopic features of focal micronodular hyperplasia: acidophilic polyhedral cells with occasional cytoplasmic vacuolation resembling the fasciculate layer cells [H&E, Bar= 25 µm]. C- Adenoma adrenocortical - nodule well delimitated, expansive, whitish and firm in cortical region (*). D- Microscopic features of adenoma adrenocortical: vacuolated polyhedral cells and presence of mega-karyocytes (extramedullary hematopoiesis) (red arrows) [H&E, Bar= 25 µm]. E- Carcinoma adrenocortical-neoplastic proliferation poor delimitated, infiltrative, reddish and soft diffuse in adrenal parenchyma. F- Microscopic features of carcinoma adrenocortical: neoplastic cells with high pleomorphism and presence of atypical mitotic figure (red arrow) [H&E, Bar= 50 µm].

The neoplasms observed were ACA in 44.1% (15/34) of the affected glands, pheochromocytomas in 23.5% (8/34), and adrenocortical carcinomas (ACC) in 11.7% (4/34) of the dogs. The metastases observed in 7 animals (20.5%) were hemangiosarcoma (2/10), histiocytic sarcoma (1/10), lymphoma (1/10), mammary gland carcinoma (2/10) and hepatic carcinoma (1/10). The mean age of the animals with neoplastic lesions were 10.6 years and female (24/34) were more affected as observed in table 1.

The presence of calcification, congestion, hemorrhage, hematopoiesis, inflammatory process and necrosis were evaluated in the cases of diffuse and nodular hyperplasia and neoplastic lesions as observed in Table 2. In the cases of hyperplastic disorders and ACA, the inflammation observed was lymphocytic, since in ACC, metastasis and pheochromocytoma cases, the inflammatory process observed was predominantly neutrophilic.

DISCUSSION

The adrenal glands have an important role in the endocrine homeostasis and can be affected by several diseases in association or not to systemic alterations [21]. In this study, 5.5% of the dogs submitted to necropsy showed histological changes in the adrenal glands. The non-neoplastic and neoplastic changes were observed in 3.2% and 2.3% of the dog population, respectively. The data in veterinary literature about the frequency of non-neoplastic changes in adrenal gland of dogs are scarce [15] or focus only the incidence of nodular hyperplasia [25]. The frequency of primary neoplastic changes in the adrenal gland was 1.8 %

(27/1454) in the population evaluated. This frequency observed was upper than 0.17% to 0.76% reported in the veterinary literature [25]. Previous studies described the incidence of adrenal tumors (primary and metastatic) accounting for 1.2% to 1.5% of all canine tumors [4,28].

Table 2. Histopathological features observed in hyperplastic and neoplastic lesions in adrenal glands of 80 dogs.

Specific adrenal disorder	Calcification % (x/n)	Congestion % (x/n)	Inflammation % (x/n)	Hematopoiesis % (x/n)	Hemorrhage % (x/n)	Necrosis % (x/n)
Non-neoplastic						
Diffuse hyperplasia	0%	13.6% (3/22)	4.5% (1/22)	0%	4.5% (1/22)	0%
Nodular hyperplasia	0%	20% (2/10)	20% (2/10)	0%	10 % (1/10)	0%
Neoplastic						
Adrenocortical adenoma	26.6% (4/15)	73.3% (11/15)	13.3% (2/15)	66.6% (10/15)	53.3% (8/15)	6.6% (1/15)
Adrenocortical carcinoma	0%	75% (3/4)	75% (3/4)	0%	75% (3/4)	100% (4/4)
Metastasis	0%	57.1% (4/7)	28.5% (2/7)	0%	57.1% (4/7)	14.2% (1/7)
Pheochromocytoma	0%	75% (6/8)	25% (2/8)	0%	25% (2/8)	12.5% (1/8)

(x/n): x= number of adrenal gland with the histopathological change; n= total number of adrenal glands with the diagnosis.

The higher incidence of adrenal changes observed in middle-aged to old-aged dogs was previously described [5,15] and was similar to observed in our data. In addition, pure breed dogs and females were more affected by adrenal changes and reflected the features of the canine population necropsied during the period. In this study, only 8.7% (7/80) of the animals presented clinical signs associated to cortical or medullar hormonal overproduction. The clinical signs of Cushing's disease were observed in five dogs (6.2%), hypoadrenocorticism in one (1.2%) and adrenalin hypersecretion in one animal (1.2%). No specific clinical sign of adrenal changes was observed in 96.2% (73/80) of the dogs. Therefore, the most of adrenal glands changes were observed during the necropsy examination. In humans [10,17] and domestic animals [25], the non-functional lesions present in the adrenal observed during image or necropsy examination are called incidentalomas. The lack of endocrine manifestations in some adrenocortical tumors, particularly carcinomas as observed in our four cases of ACC, could be explained by the fact that the malignant process is often accompanied by a deletion in some of the enzymes required for cortisol synthesis [30].

In the present study, non-neoplastic lesions (57.5%) were more frequent than neoplastic alterations (42.5%) in the 80 dogs. The hyperplastic alterations were the most frequent non-neoplastic changes representing 40% (32/80) of all adrenal lesions observed. The diffuse hyperplasia was observed in 27.5% (22/80), nodular hyperplasia in 12.5% (10/80) and representing 1.5% and 0.7% of all dog population submitted to necropsy examination differing from previous reports [15,25] which demonstrated a higher frequency of nodular hyperplasia compared to others adrenal changes. The main histopathological finding associated to diffuse hyperplasia was congestion (20% of the cases) and in 20% of the nodular hyperplasia showed congestion and lymphocytic inflammation. Our data showed no histopathological finding with high frequency in the cases of hyperplastic changes.

Diffuse hyperplasia is characterized by the cortex thickening without nodular formation, while hyperplastic nodules can be classified as micronodular (less than 0.5 cm in diameter) or macronodular (more than 0.5 cm in diameter) and can be distributed in a focal, multifocal or diffuse pattern [8]. Histologically, the hyperplastic cells showed polyhedral cells with acidophilic cytoplasm to vacuolated large cells resembling the cells of glomerulosa and fasciculata zona [6]. The hyperplastic nodules were not surrounded by a capsule of fibrous connective tissue. This feature is important to differential diagnosis from ACA [5].

Considering nodular hyperplasia, the multifocal micronodular and macronodular multifocal pattern were

the most frequent representing 40% and 30 %, respectively. There are no data in the veterinary literature about the frequency of nodular hyperplastic subtypes and association with endocrine disorders. The classification of hyperplasia in humans is an important tool. Some studies showed that macronodular hyperplasia is associated with Cushing's syndrome [11], while micronodular hyperplasia is associated to Carney Complex (multiple neoplasia syndrome) [1]. In addition, diffuse hyperplasia is commonly observed in congenital adrenocortical hyperplasia and pituitary or ectopic adrenocorticotropic hormone (ACTH) hypersecretion [14].

The frequency of neoplastic changes observed in the present study was higher compared to available data in the literature [25], representing 42.5% of adrenal changes. The ACA was the most common primary tumor observed in dogs with adrenal changes (18.7%) and affected 1% of the total population evaluated. Studies showed a frequency of 8% to 58% of ACA in dogs with adrenal tumors [15,25,28]. In the present study, the ACAs represented 44% of the adrenal tumors cases. Microscopically, the ACA are characterized by vacuolated large cells with vesicular nuclei and distinct nucleoli disposed in nests and cords arrangements, and scarce mitotic figures. The well differentiated cells suggest an origin from the zona fasciculata [5,6].

The ACC was observed in 11.7% of the dogs with neoplastic changes affecting 0.27% of the dog population necropsied in this study. Previous studies showed a frequency of 18% to 22% of ACC in dogs with neoplastic changes in the adrenal glands [7,25,28]. In the histopathological evaluation in our study, three cases of ACC presented well-differentiated neoplastic cells and one case showed high cellular pleomorphism and mitotic index, atypical mitosis and binucleation. Despite the mild histopathological malignancy features observed in two ACC, the animals showed focus of metastases in lung, kidney and central nervous system. Invasion of the adrenal capsule and blood vessels by the neoplastic cells are features described in the literature [5] and were present in all cases of ACC. However, invasion of the posterior vena cava wall and the adventitial layer of the abdominal aorta [20,22] were not observed. In humans, the most common sites described of metastasis of ACC were the regional lymph nodes, peritoneal and pleural surfaces, liver, lung and bone [19,30] and were associated to trabecular and diffuse growth pattern of neoplastic cells in the ACC tumor. In our study, the three metastatic cases of ACC showed diffuse and trabecular growth pattern,

however, there are no data in the literature associating the histological pattern with a metastatic behavior in animals. Metastases to distant sites are rare and were described in liver, lung, kidney, nervous system and mesenteric lymph nodes of dogs [5,16,22,31,32].

The adrenal glands with ACA showed multifocal areas of extramedullary hematopoiesis (66.6%) associated with congestion (73.3%) and hemorrhage (53.3%) and the main histopathological findings found in ACC were necrosis (100%), congestion (75%), hemorrhage (75%) and inflammatory infiltrate (75%). These results showed that necrosis and inflammatory infiltrate were features of ACC and may be used in the differential diagnosis of ACA.

The diagnosis of pheochromocytoma was observed in 23.5% of the dogs with adrenal neoplasia and the incidence in the analysed population was 0.55%. Previous studies showed a frequency of tumors (neuroendocrine origin) in the medullar region varying from 8% to 22% in dogs with adrenal tumors [15,25,28], accounting for 0.01% to 0.1% of all canine tumors [12]. However, there are no data focusing on the frequency of pheochromocytoma in dogs. According to the veterinary literature, more than 50% of these tumours are malignant and invade through the capsule of the adrenal gland into adjacent caudal vena cava [2,5,21]. In the present study, this finding was observed in 25% (2/8) of the dogs.

Metastasis to adrenal glands have been reported in 30% of human patients and the bilateral involvement is observed in 50% [8,24,27]. In dogs, the rate of metastasis to the adrenal was reported in 21% with bilateral involvement in 55% of the oncologic patients [18]. In our study, we observed that metastasis accounted for 20.6% of the neoplastic changes in adrenal glands and bilateral involvement occurred in 42.8%. On the other hand, frequency rates of adrenal metastasis varying from 3 to 5% in dogs with adrenal tumours was also reported [25,28].

CONCLUSIONS

The results of the present study showed a prevalence of non-neoplastic and non-functional disorders in the adrenal, mainly diffuse and nodular cortical hyperplasia. The most of adrenal changes were necropsy findings and the histopathological evaluation was fundamental to definitive diagnosis of the adrenal disorders.

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