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Case Report

Pheochromocytoma in a Dog as a Cause of Aortic Thromboembolism

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Abstract

A thirteen-year-old female German Spitz dog was referred to Veterinary Hospital of the Universidade Estadual de Londrina, with acute paraplegia and pain in pelvic limbs for two days. The clinical sings, as lack of femoral pulse and cold distal limbs, were consistent with ischemic neuromyopathy due to aortic thromboembolism. Soon after the examination, she had a severe epistaxis and died. On postmortem examination it was observed a thrombus adhered to the aorta trifurcation and a mass occupying the position of the right adrenal gland, which was diagnosed as pheochromocytoma on histological and immunohistochemistry examinations.

Key Words: dog, ischemic neuromyopathy, adrenal tumor, immunohistochemistry

Introduction

Pheochromocytomas, or chromaffin cell tumors, appear to be rare, constituting only 0,13-0,01% of all canine tumors (6, 13, 16, 19), but they are the second most common adrenal neoplasm in dogs (17). Pheochromocytomas are benign histologically, slow-growing, potentially functional, and noninvasive neoplasms (3). They are occasionally malignant with metastasis to distant organs (13, 17)

Clinical signs are usually related to the catecholamine release, and it's depending of the kind of receptors α and β adrenergic classes stimulated (Table 1). (1, 6, 7, 12-14, 17). Pheochromocitomas occasionally result in secondary conditions like thrombosis of the caudal vena cava and aortic thromboembolism, which occurs due to the endothelial damage, blood stasis and hypercoagulable states (2, 8-10, 19).

Table 1: Clinical signs associated with pheochromocytoma (12)

Non-specific	Cardiopulmonary	Neurological	Miscellaneous
weight loss, anorexia, depression, weakness, collapse, restlessness	dyspnoea, panting, cough, exercise intolerance, cyanosis, epistaxis	seizures, paraparesis, ataxia, dilated pupils	polyuria/polydipsia, abdominal distension, diarrhoea

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Diagnosis of pheochromocytoma is difficult due to the lack of specific clinical findings and low index of suspicion of the disease, thus requiring familiarity with the syndrome. General signs (table 1) of weight loss, anorexia and depression are frequently reported (12, 13, 17, 19). A definitive diagnosis of pheochromocytoma can only be obtained through histopathology; therefore, the diagnosis is often obtained post-morten (6, 12, 13, 16-18).

Pheochromocytomas can vary markedly in their histologic appearance so, a definitive diagnosis may depend on application of specific histochemistry, immunohistochemistry and ultrastructure techniques. However, as chromaffin granules that is detect in argyrophilic staining and electron microscopy can be scanty in some tumors, histochemistry have proven useful in identify atypical pheochromocytomas (20).

The prognosis is difficult to define precisely, as pheochromocytoma is rare and limited number of cases has been treated (11, 12)

Case report

We present a case of a thirteen-year-old female German Spitz dog that was referred to Veterinary Hospital of the Universidade Estadual de Londrina with acute paraplegia and pain in pelvic limbs for two days. Clinical evaluation showed hypothermia (36,5ºC), lack of femoral pulse bilaterally and cold distal limbs. Neurological findings included absence of conscious proprioception, tendon reflexes and pain perception in pelvic limbs. The clinical findings were consistent with ischemic neuromyopathy due to aortic thromboembolism.

The complete blood count was normal. There were liver enzyme elevations and marked proteinuria (Table 2). Thoracic radiographs revealed cardiac enlargement and interstitial pulmonary pattern and hepatomegally was seen in abdominal radiography. However, soon after the examination, she had a severe epistaxis and died.

A complete necropsy was performed. It was observed a concentric hypertrophy in the left ventricle (Fig. 1) and moderate dilatation in the right one, and also a thrombus adhered to the aorta trifurcation (Fig. 2). The liver had a nutmeg feature. There was moderately firm, irregular, white-to-rubious mass measuring approximately 5,5 x 3,0 cm and occupying the position of the right adrenal gland (Fig. 3). The left adrenal gland was mild enlarged and irregular (Fig. 3).

On histological examination of formalin-fixed paraffin-embedded tissue, the cells were cuboidal with moderate to abundant amphophilic cytoplasm and round to oval nuclei with coarsely granular chromatin with medium mitotic figures, which was diagnosed as pheochromocytoma in adrenal (Fig. 4A) with micrometastases in the liver.

By immunohistochemistry, the tumor cells were intensely immunoreactive for Synaptophysin (SYN) and Chromogranin A (CGA) (Fig. 4B and 4C) and poorly imunoreactive to neuron-specific enolase (NSE) (Fig. 4D).

Table 2: Biochemical laboratory tests and urinalysis performed from the female dog with ischemic neuromyopathy due to aortic thromboembolism

Routine laboratory	Results	Reference
Biochemical		
Alanine aminotransferase (ALT)	703U/l	17-87U/l
Alkaline phosphatase (ALP)	448U/l	12-110U/l
Total protein	6,8g/dl	6-8g/dl
Albumin	2,76g/dl	2,6-3,3g/dl
Creatinine	1,05mg/dl	0,5-1,6mg/dl
Urinalysis		
Density	1028	1015-1045
pH	6,0	5,5-7,0
Protein	(++)	--
Leukocytes	2/field	1-2/field
Red blood cells	15/field	1-2/field
Granulose cylinder	1/field	--
Bladder cells	present	--

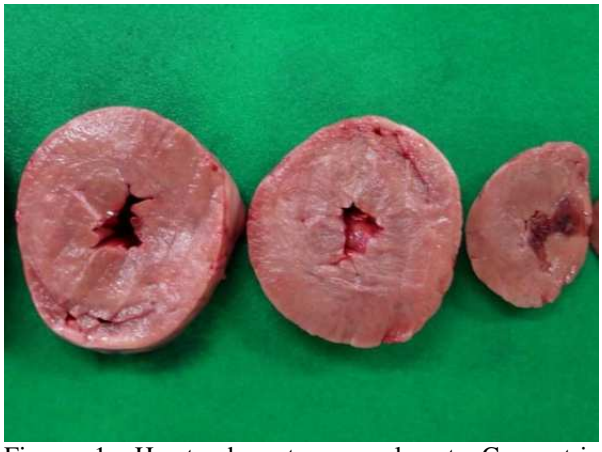


Figure 1: Heart, dog, transversal cut. Concentric hypertrophy in the left ventricle.

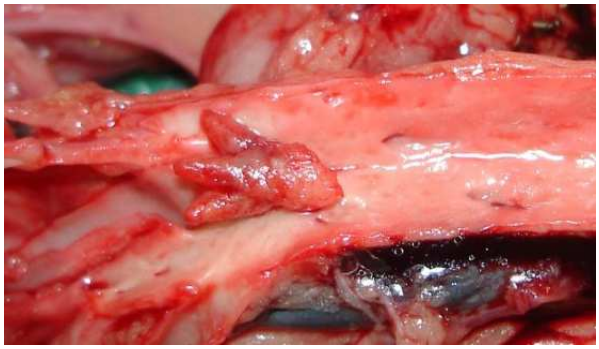


Figure 2. Thrombus, lodged at the aorta trifurcation, dog with pheochromocytoma.

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Figure 3. Kidneys and adrenal glands, dog with pheochromocytoma. Right kidney (RK) and right adrenal gland (RAd) with a moderately firm, irregular, white-to-rubious mass measuring approximately 5,5 x 3,0. The left adrenal gland (Lad) was mild enlarged and irregular.

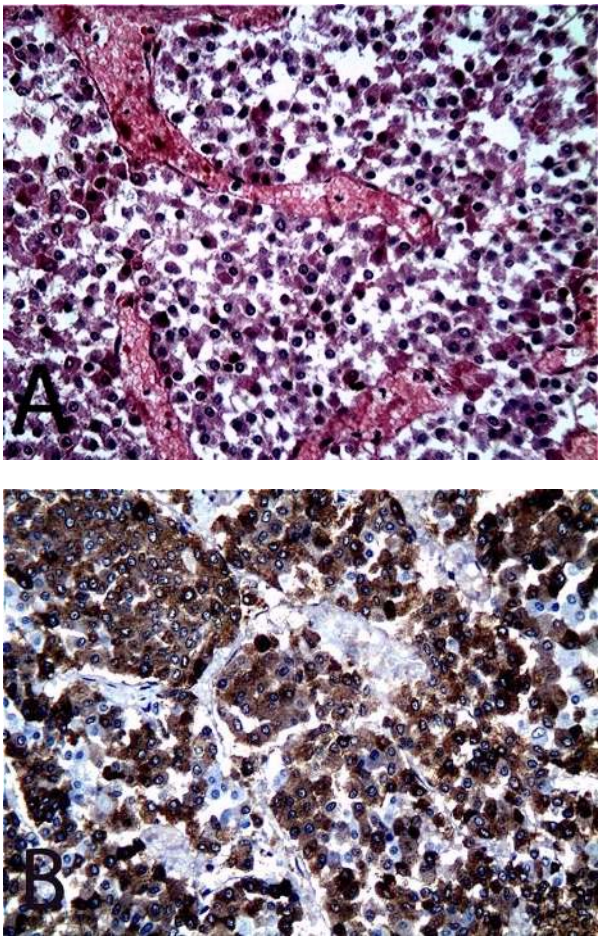


Figure 4. A: Adrenal gland. Cuboidal cells with moderate to abundant amphophilic cytoplasm and round to oval nuclei with coarsely granular chromatin with medium mitotic figures. Hematoxylin-Eosin. B: Pheochromocytoma, dog, stained with Synaptophysin antibody showing intense immunoreactivity. C: Pheochromocytoma, dog, stained with Chromogranin A antibody showing intense immunoreactivity. D: Pheochromocytoma, dog, poorly imunoreactive to neuron-specific enolase (NSE).

Discussion

We diagnosed ischemic neuromyopathy due to aortic thromboembolism because of clinical signs of absent femoral pulse and cold distal limbs. This disorder is rare in dogs and commonly a complication of another disease, including dirofilariasis, neoplasia, idiophatic thromboembolic disease, hyperadrenocorticism, disseminated intravascular coagulation, sepsis, autoimmune hemolytic anemia, arteriosclerosis, protein-losing enteropathies and nephropathies, bacterial endocarditis and cardiac disease (2, 4, 5, 8, 10, 19).

Occlusion of the aortic trifurcation, as we seen in the present case, obstructs internal and external iliac arteries and the median sacral artery which cause muscle ischemic myopathy, axonal degeneration and ischemic muscle contracture. Aortic thromboembolism is more common in the cat where it is usually

associated with dilated or restrictive cardiomyopathy and leads to acute hindquarter paresis with pain, rhabdomyolysis, signs of peripheral vascular occlusion, and more serious systemic illness (4).

Physical examination findings in animals with pheocromocytoma are usually non-specific (1, 12, 17) as seen in this case. The results of routine laboratory work, including complete blood count, biochemical profile, and urinalysis, were non-specific (12, 17). Liver enzyme elevation was present but according to descriptions, it does not appear to correlate with the presence of hepatic metastases (12), but it can be consequence of hepatic hypertension (6). It is important to remember that in this case, there was metastase in the liver.

Proteinuria was found and presumably it results from hypertensive glomerulopathy (12). Loss of antithrombin III through glomerular disease induced by hypertension may increase the thrombotic risk for these patients (10). Besides this, any neoplasia can be a common cause of hypercoagulability with a multifactorial etiology, as platelet hyperaggregability and the inhibition of the fibrinolytic system (10). These factors could contribute to the development of the thrombus as seen in this report.

Radiographs of the abdomen can reveal a mass in perirenal area in 30-56% of cases (12), which in this case didn't occur. Thoracic radiographs can reveal changes secondary to hypertension, including cardiac enlargement, as seen in this case, and pulmonary congestion or oedema (6, 12).

Ultrasonography can be helpful in identifying an adrenal mass in cases of suspected pheochromocytoma (17) but it is limited in determining the extent of the disease (6, 12). In this case, due to hyperacute presentation, it was not held.

Determination of blood pressure is indicated in any dog with suspected pheochromocytoma and demonstration of hypertension would be supportive of the disease (12, 16, 17). Unfortunately it was not determined in this case, but the severe epistaxis that precedes the death could be the result of a hypertensive crisis. However, the failure to document systemic hypertension does not rule out pheochromocytoma (14).

Large tumors may exert pressure on adjacent organs or vessels, and that regional invasion of the caudal vena cava may be seen in up to one third and distant metastases in up to half of afflicted dogs (3, 12, 17) but was not seen in the present report. This invasive form cause a variety of extra-adrenal manifestations including venous distention, pain and hind limb paraparesis or paraplegia secondary to vascular compromise as well as primary neurological abnormalities (3, 12). In 13 dogs with tumor trombi, the mass was confined to the phrenicoabdominal vein in three dogs, a local caval thrombus was found in eight dogs, and an extensive caval thrombus was found in two dogs (11).

Surgery is the treatment of choice for pheochromocytoma in dogs (11, 12, 15, 16). However, resection of these tumors tends to be problematic because many of these animals have a high anaesthetic risk as a result of hypertension and arrhythmias, which may worsen with surgical manipulation (11, 12).

As in the present paper, a large proportion of pheochromocytomas (38–48%) are diagnosed at post-mortem examination (2, 3, 13, 17): in a description of six dogs with pheochromocytoma, two had collapsed suddenly and died before diagnostic tests could be performed (7), and in another report a dog died shortly after the initial onset of clinical signs (2).

Because pheochromocytomas can vary markedly in their histologic appearance, a definitive diagnosis may depend on application of specific immunohistochemistry, and ultrastructure techniques. Immunohistochemical evaluation using antibodies against various neuropeptides is useful for confirming the chromaffin cell origin of neoplasms in humans and dogs (1). CGA and SYN are usually detected in neoplastic cells of adrenal pheochromocytomas in dogs, as in the present paper (18).

Pheochromocytoma is a rare disorder that should be consider as possible cause of aortic thromboembolism. Both complaint have poor prognosis and together make the treatment more laborious due to the difficult to remove or dissolve the thrombus. Treatment would include anticoagulant therapy and maybe surgical embolectomy, but this is associated with high rate of mortality (10). In a preview report, five dogs were euthanized at the owner's request following a recurrence of clinical signs consistent with a second thromboembolism (2). Perhaps with more awareness of this condition, it can be diagnosed and managed more successfully.

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