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Neoplastic disease

Phaeochromocytoma associated with cardiomyopathy and leukocytoclastic vasculitis in a dog

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Abstract

Phaeochromocytomas are rare tumours of the adrenal medulla that can be associated with various presentations. Many of the better characterized clinical signs, including weakness, tachycardia and tachypnoea, are attributable to excessive and unregulated catecholamine secretion from functional tumours. In addition to catecholamine-induced cardiomyopathy and vasospasm, the invasive nature of phaeochromocytomas can lead to occlusion of the caudal vena cava contributing to systemic cardiovascular compromise. In humans, leukocytoclastic vasculitis is a rarely reported manifestation of catecholamine excess associated with phaeochromocytomas. We now describe a dog that had an invasive unilateral phaeochromocytoma with histological evidence of myocardial damage, consistent with catecholamine-induced cardiomyopathy, and leukocytoclastic vasculitis of small vessels in a range of tissues. We conclude that catecholamine excess may have played a role in the pathogenesis of vasculitis in this case. To the best of our knowledge, this is the first documented association between phaeochromocytoma and leukocytoclastic vasculitis in a non-human species.

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Phaeochromocytomas are rare tumours originating from the chromaffin cells of the adrenal medulla. Less commonly, tumours of chromaffin cells can arise in sympathetic or parasympathetic ganglia at extra-adrenal sites, where they are termed paragangliomas. In veterinary species they have been best described in dogs, horses and exotic animals. In dogs, the clinical and pathological features of phaeochromocytomas share similarities with human cases [1]. They typically present unilaterally (approximately 90%), although simultaneous occurrence with other endocrine tumours has been reported [2,3], reminiscent of multiple endocrine neoplasia in humans. In cattle, but have been documented in a wide range of other domestic and exotic animals. In dogs, the clinical and pathological features of phaeochromocytomas share similarities with human cases [1]. They typically present unilaterally (approximately 90%), although simultaneous occurrence with other endocrine tumours has been reported [2,3], reminiscent of multiple endocrine neoplasia in humans. In humans, heritable, autosomal dominant mode of inheritance has been described in at least some other non-human species, including multiple endocrine neoplasia in bulls [4,5].

Malignancy of phaeochromocytomas is poorly correlated with histological appearance [1], as neoplastic cells may be histologically identical to normal chromaffin cells or markedly pleomorphic. Instead, malignant tendencies are more likely to be indicated by large size and invasive behaviour. On the other hand, distant metastases may occur in cases without evidence of local infiltration of the adrenal capsule or adjacent vascular structures. In a study of 50 canine phaeochromocytomas, approximately 50% were associated with local invasion of the vena cava, 24% had distant metastasis and 12% had regional lymph node involvement [6]. Similar proportions were found in a subsequent retrospective study of 61 canine cases [7]. Metastasis occurs to a wide range of tissues; liver, lung, spleen, kidney and bone are among the most commonly reported sites [6,7].

Pathological consequences of phaeochromocytomas can manifest through space-occupying effects, local invasion, distant metastases or catecholamine production. Approximately one-third of canine phaeochromocytomas are considered clinical, although presenting signs do not necessarily reflect functionality [7]. Chromaffin cells of the adrenal medulla are neuroendocrine cells that synthesize and store catecholamines (norepinephrine, epinephrine and dopamine), which they release in response to cholinergic stimulation. In this manner they act as an interface between nervous and endocrine control. Consequently, neoplastic cells in functional phaeochromocytomas, in which hormone release is disassociated from this control, have systemic metabolic and...
haemodynamic influences that can be associated with a multitude of clinical manifestations indicative of catecholamine excess.

A 9-year-7-month-old, male neutered Golden Retriever dog was referred following primary presentation for investigation of polyuria, polydipsia and urgency to urinate. Urinalysis had raised suspicion of a protein-losing nephropathy. Two weeks after initial presentation to the primary veterinary practitioner, the patient had a stress leukogram, worsening azotaemia, tachycardia and tachypnoea, reduced peripheral pulse quality and a tense abdomen, and was subsequently referred for further investigations. Thoracic and abdominal ultrasound revealed pericardial and peritoneal effusions, hepatic congestion and a large left adrenal mass with an intravascular component that obliterated the caudal vena cava lumen. Echocardiography revealed mild tamponade and elevated venous pressure, thickening of the right auricle and mitral valve and hypertrophy of the left ventricular wall, which had poor systolic function and heterogeneous echogenicity. The electrocardiogram was consistent with sinus rhythm with frequent ventricular premature complexes, runs of accelerated idioventricular rhythm and brief episodes of ventricular tachycardia up to 200 bpm with R on T morphology. Cardiac troponin I was elevated above the level of quantification (>50 ng/ml). Given the extent of the adrenal mass with concurrent cardiovascular disease, the prognosis was considered poor and euthanasia was elected.

On post-mortem examination the left adrenal gland presented as an enlarged, smooth, encapsulated 3 × 3 cm well-demarcated mass. Consistent with the sonographic findings, the adjacent vena cava was distended up to 4 cm in diameter, for a length of approximately 6 cm, by a firm, friable, dark red intraluminal extension of the expansile adrenal tissue, which penetrated through the vessel wall. The intra-abdominal and retroperitoneal adipose tissue was firm and reddened, the spleen was pale and contracted and the liver was pale, with rounded edges and a prominent reticular pattern. The pericardium was firm, thickened and opaque, with yellow to green roughening on the parietal and visceral surfaces, and contained a large volume of serosanguineous fluid.

Samples from a range of tissues (stomach, small and large intestines, spleen, lungs, heart, pericardium, pancreas, kidneys, perirenal adipose tissue, adrenal glands and caudal vena cava) were fixed in 10% neutral buffered formalin. Fixed tissues were processed routinely, paraffin embedded and 4 μm sections stained with haematoxylin and eosin (HE) for microscopic evaluation. Selected samples from the adrenal mass were immunolabelled for chromogranin A (rabbit monoclonal; 1:400; Abcam, www.abcam.com) and synaptophysin (mouse monoclonal; 1:50; Dako, www.agilent.com).

Histologically, the adrenal neoplasm was composed of a mostly expansile, multifocally infiltrative, densely-cellular proliferation of small polygonal cells arranged in delicate packets and cords, interwoven by a fine fibrovascular stroma, which expanded the adrenal medulla and compressed the residual cortical tissue (Fig. 1). The neoplastic cells comprised a monomorphic population, with a small to moderate amount of non-staining to finely granular, slightly eosinophilic cytoplasm, and variably defined intercellular borders. Their nuclei were small and round, with densely clumped, hyperchromatic chromatin and indistinct nucleoli. Mitotic figures were rare. Multifocal to coalescing haemorrhages were present throughout the tumour. Multifocally, the neoplastic cells breached the adrenal capsule and infiltrated periadrenal connective tissue and the adjacent wall of the vena cava, and expanded and occluded the lumen. An organized fibrin thrombus was adherent to the luminal proliferation. The neoplastic cells had strong cytoplasmic immunoreactivity for chromogranin A (Fig. 2) and synaptophysin (Fig. 3).

There were widespread haemorrhages within the perirenal adipose tissue, the pericardium and epicardium and the urinary bladder mucosa. Multifocally, small to medium arterioles were

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Fig. 1. Phaeochromocytoma, left adrenal gland, dog. Invasive adrenal mass composed of neoplastic cell population with characteristic neuroendocrine packetting. Adrenal cortical cells compressed against adrenal capsule (right). HE. Bar, 250 μm.
occluded by fibrin thrombi and most had fibrinoid necrosis, characterized by an intensely eosinophilic circumferential collar with loss of endothelial detail and scattered leukocytoclastic debris (Fig. 4). The left ventricular myocardium had moderate to severe, chronic, multifocal myocardial degeneration and necrosis with mild lymphohistiocytic myocarditis.
The histopathological findings confirmed a diagnosis of pheochromocytoma, which was consistent with the gross appearance and clinical presentation.

This case is noteworthy due to the association between the pheochromocytoma and systemic leukocytoclastic vasculitis involving small and medium vessels in several tissues, most prominently in the perirenal adipose tissue, pericardium and epicardium. Restrictive-effusive pericarditis probably explains the degree of cardiac tamponade apparent echocardiographically and the serosanguineous effusion seen at necropsy. Rare descriptions of paraneoplastic, catecholamine-induced pericardial effusions presenting with inflammatory histopathology have been documented in humans [8,9]. Fibrinoid necrosis of small vessels, endothelial cell swelling, extravasation of erythrocytes and leukocytoclasis are characteristics of necrotizing hypersensitivity vasculitis, which typically manifests in cutaneous capillaries and venules and, much less commonly, involves extracutaneous vessels [10]. Various aetiologies are known triggers for leukocytoclastic vasculitis, including infections, pharmacotherapies, connective tissue diseases and several neoplastic conditions [10]. In humans, leukocytoclastic vasculitis is the most common manifestation of paraneoplastic vasculitis; almost 20% of patients with this presentation have a concurrent malignant condition. Overall, when other types of vasculitis are considered, coexistence with neoplasia occurs in only around 2.5–5% of cases and paraneoplastic vasculitis is more commonly associated with haematological rather than solid tumours [11,12].

Solans-Laquè et al [11] briefly reviewed medical reports of solid tumours associated with leukocytoclastic vasculitis (among other vasculitides), and found that the most common were renal carcinomas (11/43; 26%), lung carcinomas (7/43; 16%), colon adenocarcinomas (5/43; 12%) and breast carcinomas (5/43; 12%). Pheochromocytomas are implicated in inflammatory presentations, whereby chronic catecholamine excess leads to elevated inflammatory markers producing lesions such as polyserositis (including pericarditis) and fever [8,13]. Catecholamine-induced paraneoplastic vasculitis, which includes cerebral vasculitis and small vessel cutaneous leukocytoclastic vasculitis, has been described as a rare manifestation [8,14–16]. Although the pathogenesis is undefined, vasculitis may result from catecholamine-induced haemodynamic damage to vessel walls in conjunction with an autoimmune mechanism. A definitive role for catecholamine excess in triggering an autoimmune process is suggested by the resolution of symptoms of Behçet’s disease (multifocal vasculitis of unknown origin) following surgical excision of pheochromocytomas [9,14,16]. Furthermore, catecholamine-excess has been implicated in other autoimmune conditions (eg, systemic lupus erythematosus) in association with pheochromocytomas [17].

As well as restrictive pericarditis, marked neoplastic thrombosis impeding vena caval return would have added to the poor haemodynamic status of this dog. Furthermore, this case exhibited severe, multifocal to coalescing myocardial degeneration and necrosis. These changes would have contributed to the clinical, imaging and post-mortem signs consistent with congestive heart failure (hepatic congestion and abdominal effusions). These changes would have contributed to the clinical, imaging and post-mortem signs consistent with congestive heart failure (hepatic congestion and abdominal effusions). Catecholamine-induced cardiomyopathy is known to occur in humans secondary to prolonged excessive catecholamine secretion by neoplastic tissue and has also been described in a retrospective study of nine dogs with functional pheochromocytomas [18]. Catecholamines exert haemodynamic effects on the cardiovascular system by binding to α-adrenergic and β-adrenergic receptors. Chronic excitation of β1-adrenergic receptors, which are located in the sinoatrial and atrioventricular nodes and cardiac myocytes, leads to a sustained increase in contractility and heart rate. Although activation of β2-adrenergic receptors in cardiac and vascular tissues leads to myocardial relaxation and vasodilation,

Fig. 4. Pheochromocytoma, left adrenal gland, dog. Small vessel vasculitis characterized by thrombosis and fibrinoid necrosis of a small arteriole in perirenal adipose tissue. Leukocytoclastic debris in vessel wall (arrowheads). Adjacent vein unaffected. HE, Bar, 100 μm.
these effects are superseded at high and excessive catecholamine levels. Ultimately, desensitization of β1-adrenergic receptors and catecholamine-induced calcium influx into cardiac myocytes contribute to decompensation and heart failure [19]. The chronically elevated myocardial activity creates an oxygen demand/delivery mismatch that results in ischaemia. Furthermore, norepinephrine-induced activation of α-adrenergic receptors on vascular smooth muscle leads to vasoconstriction and vasospasm of the coronary arteries, which can result in infarction [20]. Systemic hypertension via the same mechanisms may exacerbate the effects of the direct toxicity of catecholamines and their metabolites on the myocardium. It has been suggested that the greater vasoconstrictive properties of norepinephrine compared with epinephrine may induce increased vascular damage in human cases of norepinephrine-secreting pheochromocytomas, indicating a greater risk for vascular complications [14]. Norepinephrine is the predominant catecholamine in young dogs, but the balance shifts towards epinephrine in normal adult dogs. Interestingly, norepinephrine is the main catecholamine associated with tumour tissue in canine pheochromocytomas [21]. Immunohistochemical labelling using antibodies to dopamine β-hydroxylase or phenylethanolamine-N-methyl transferase – enzymes responsible for biosynthesis of norepinephrine and epinephrine, respectively – can be used to demonstrate the nature of catecholamines present in neoplastic cells [22,23]. Ultrastructural characteristics of secretory granules in chromaffin cells can also be used to differentiate between norepinephrine or epinephrine-producing cell types [21,24].

The conclusions from this case have several limitations. As haematological measurements of catecholamines were not available, the deduction that the pheochromocytoma was functional is presumptive. Similarly, immunohistochemical characterization for catecholamine-producing enzymes was not done. Nevertheless, the clinical signs and myocardial presentation were highly suggestive and, in the absence of other explanatory pathologies, consistent with catecholamine excess. As far as we are aware, the presence of florid fibroinoid necrosis and leukocytoclastic vasculitis in the perirenal adipose, pericardial and epicardial tissues is the first evidence of apparent pheochromocytoma-associated catecholamine-induced vasculitis in a non-human species.

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Declaration of competing interests

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