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Case report

Acute Onset Of Hypertensive Encephalopathy In A Dog With Right Adrenal Pheochromocytoma And Neoplastic Invasion Of The Caudal Vena Cava: case report and review of the literature.

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Abstract: Pheochromocytoma in dogs is a rare tumor of the adrenal medulla. Clinical signs are often intermittent and vague, resulting of an intermittent catecholamine over-secretion or neoplastic invasion of adjacent structures. A 12 years old Epagneul Breton with a one year history of CKD, was examined for an acute onset of severe neurological signs. Based on clinical and instrumental data hypertensive encephalopathy was suspected, and a cardiac and abdominal ultrasound were performed. A severe hypertensive cardiopathy and a 1 cm right adrenal gland mass with invasion of caval vena cava were diagnosed. Computed tomography imaging confirmed the suspect of invasive malignant neoplasia and an emergency pharmacological therapy was started to reduce the systemic pressure, improve clinical signs and stabilize the dog in view of a surgical resolution. After an initial improvement the general condition of the patient abruptly worsened, and euthanasia was elected. Histology examination confirmed a PCC of right adrenal gland, invading the CVC. To the authors conclusions acute hypertensive encephalopathy is a peculiar form of presentation for PCCs. Ultrasound is a useful rapid and economic test to suspect PCC as it can detect adrenal alterations, caval invasion, metastasis and cardiac sequelae consistent with the condition. PCC can mime multiple affections, and can be misinterpreted, especially when a concurrent disease has already been diagnosed. Veterinarians need to be aware that comorbidities (i.e. CKD) could mask clinical signs and delate the diagnosis.

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1. Introduction

Pheochromocytomas (PCCs) are catecholamine-producing neuroendocrine tumours that arise from the chromaffin cells (pheochromocytes) of the adrenal medulla or sympathetic paraganglia [1]. Usually, this rare tumour is solitary and is located in or about the adrenal gland [2]. It can be benign or malignant and may be functionally active or inactive [3]. When active, PCCs can produce and excrete the polypeptide hormones epinephrine, norepinephrine, and occasionally dopamine. When non-active they can still be capable of producing clinical signs by virtue of their space-occupying nature [2]. Therefore, clinical signs either result from the neoplastic production of catecholamines (e.g., episodic weakness, restlessness, tachycardia, hypertension, and collapse), or from the space-occupying nature of the tumour. PCCs affect middle-aged to older dogs with no gender or breed predilection. Because of the vague nature of their manifestations, they frequently are diagnosed as an incidental finding in dogs and in human beings [4-7]. Based on the rarity of the condition, the

difficulties in ante mortem dignosis and the low number of cases reported, additional reporting to describe clinical aspects of diagnosed PCC in dogs is indicated.

The aim of this study is to report a clinical case of an acute onset of hypertensive encephalopathy in a dog with right adrenal PCC and neoplastic invasion of the caudal vena cava (CVC) with a brief review of the literature.

2. Case history

A 12-year-old spayed female Épagneul Breton, weighing 14.5 kg, was examined at the Veterinary Medical Teaching Hospital of University of Bari, Italy for acute onset of central neurological clinical signs. The owner reported that the day before consulting the dog showed circling, loss of balance, disorientation, and nocturnal vocalizations. The dog had a one-year history of polyuria, polydipsia, chronic kidney disease (CKD stage II IRIS) and in the late months, progressive weight loss, and tremors.

On clinical examination, the animal was tachypnoeic, depressed with an altered mental status and ataxic, it showed right head-tilt, right drifting, and head pressing. The patient was hospitalized, and emergency laboratory tests were run, showing an increase of urea (193 mg/dL; reference interval: 15-50 mg/dL), and creatinine (2.89 mg/dL; reference interval: 0.70-1.40 mg/d). Glucose was in the reference interval (125 mg/dL; reference interval: 70-130 mg/dL), and whole count blood was normal. Repeated indirect blood pressure measurements were also taken (using SunTech Vet30) (Table1) showing a severe hypertension. EKG examination showed no abnormalities. Brain computer tomography (CT) in emergency resulted negative.

Table 1. Blood pressure values during the three days of hospitalization from treatment starting.

Day of hospitalization	Systolic (mmHg)	Diastolic (mmHg)	MAP (mmHg)
Day 1	198	127	135
	189	114	139
	166	120	128
	161	98	119
	182	113	129
Day 2	154	118	130
	170	105	126
	150	107	125
	177	117	135
	150	102	113
	154	102	108
	136	107	124
	151	98	195
Day 3	145	112	123
	161	114	121
	160	111	117

A hypertensive encephalopathy was suspected. In the differential diagnosis traumatic, toxic, and vascular central damage were also considered. Other causes, including central neoplasms, were included although less probable due to the rapid onset of the neurological signs. Being the dog a housed pet and based on the patient's medical history, the hypothesis of trauma and toxic ingestion were ruled out.

An echocardiographic evaluation was performed (ESAOTE Mylab Alpha). Left ventricular concentric hypertrophy along with aortic bulb dilatation, aortic regurgitation, and interventricular septal hypertrophy, in absence of aortic stenosis, were assessed on ultrasound (Figure1), suggesting a severe hypertensive cardiopathy.

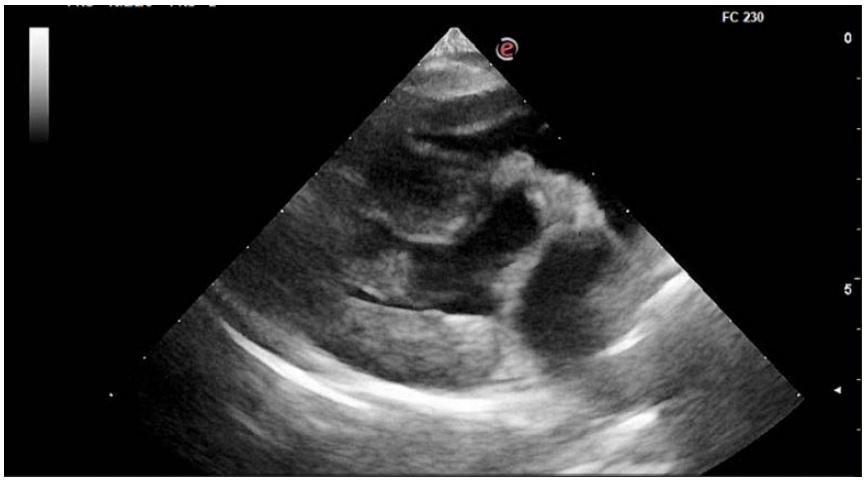

Figure 1. Interventricular septal hypertrophy.

The abdominal ultrasound examination revealed and abnormal right adrenal gland with the presence of a not-occluding structure in the lumen of the caudal vena cava (CVC). Right adrenal gland cranial pole appeared increased in volume (12x25mm), with a mixed echogenicity, dishomogeneity and an irregular profile (Figure2) with invasion of the CVC (Figure3). At colour Doppler, a reduced residual flow was documented at that site in CVC (Figure4).

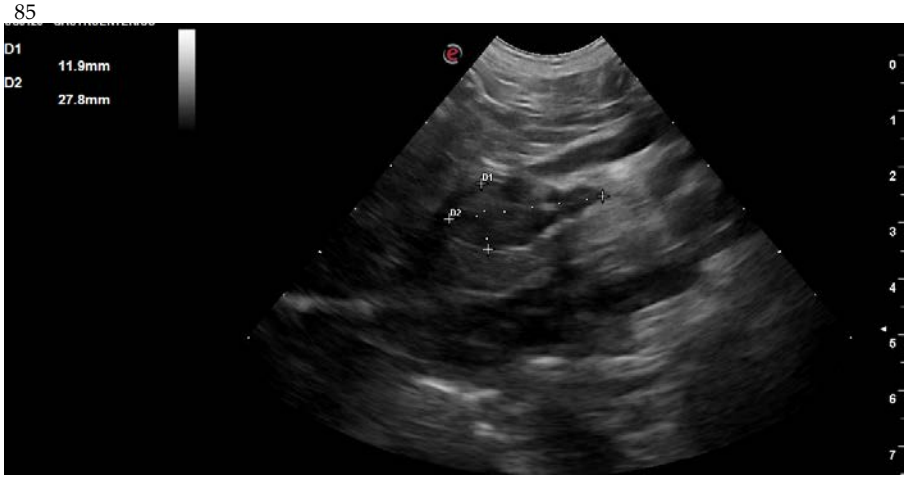

Figure 2. Right adrenal gland showed an irregular profile and dishomogeneity.

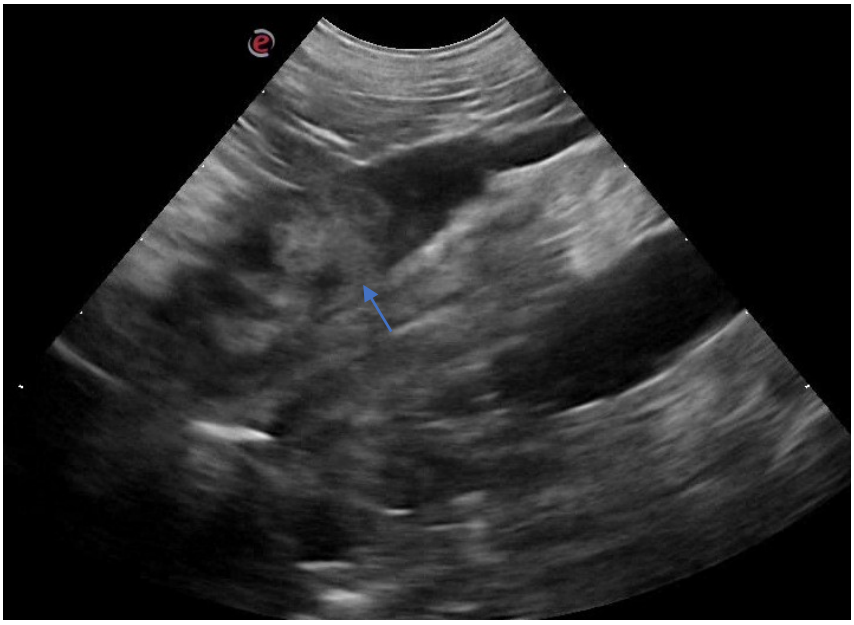

Figure 3. Structure invading CVC lumen.

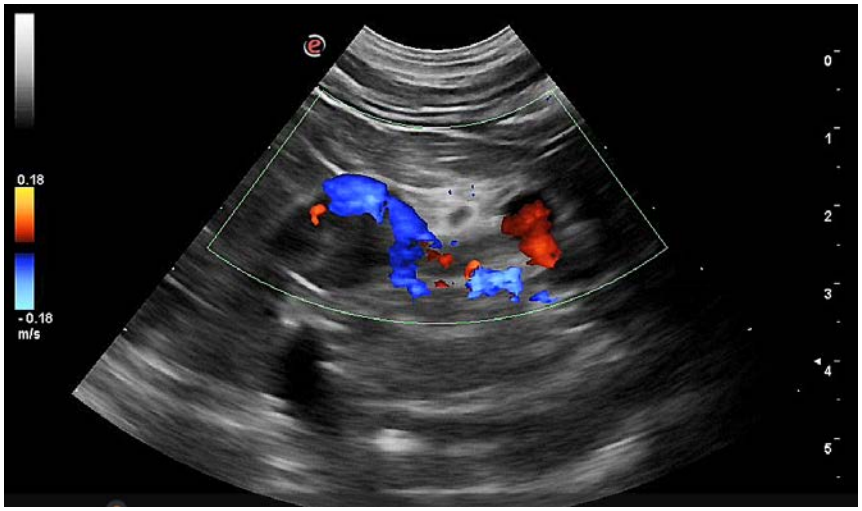

Figure 4. Color Doppler on CVC cross-section, showing a residual flow through the vessel.

An adrenal neoplasm with invasion of the CVC was suspected and it was decided to perform a total body contrast-enhanced CT investigation to better investigate the adrenal mass and the caval involvement, to evaluate other possible metastases. CT confirmed the presence of a mass at the adrenal level and a structure compatible with a neoplastic thrombus in the CVC (Figure5).

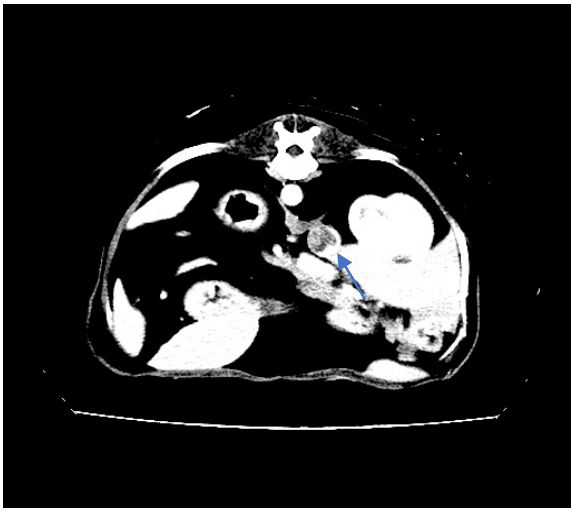

Figure 5. Structure invading CVC lumen enhanced by contrast medium.

In the meantime, the patient was hospitalized and treated with: nitroglycerin patch (10mg/sid), labetalol (0.25mg/kg/ev, then 25 μg/kg/min/CRI), furosemide (0.5 mg/kg/h/CRI), prazosin (1 mg/os), and benazepril (0,5 mg/kg/os/bid), with the aim to reduce the systemic pressure. The patient initially responded to pharmacological therapy, its general conditions improved in three days, and, on owner request, the dog was discharged pending adrenalectomy surgery decisions. At discharging, the dog was able to walk without falling, conscious and reactive to stimulus. Unfortunately, after few days at home, the clinical signs deteriorated and, in sight of the patient's general conditions, the owners elected humane euthanasia.

A necropsy was performed. In the abdominal cavity, the mass of the right adrenal gland invading the CVC was visualized. It appeared like a clear, yellowish looking neoformation. The vessel was grossly distended but it wasn't completely obstructed. A single specimen including the adrenal mass and the invaded CVC was submitted for histologic examination. Histological diagnosis confirmed the presence of right adrenal pheochromocytoma with neoplastic invasion of the CVC. A non-capsulated, not-circumscribed neoplasm that completely replaces the right adrenal medulla, compressing, and also infiltrating the adrenal cortex was described. The neoplasm was characterized by polygonal cells arranged in compact, lobules, that often were in a palisade pattern. Neoplastic cells had eosinophilic to brownish granular cytoplasm, irregularly round nuclei with finely punctuated chromatin, and distinct nucleolus. Occasionally, the neoplastic cells arranged in a palisade pattern around the blood vessels, forming sort of rosettes and they presented multifocal areas of necrosis with diffuse haemorrhagic extravasation, fibrin deposition and rare macrophages. The specimen had moderate anisokaryosis and mild anisocytosis.

4. Discussion

This report documents a case of PCC of right adrenal gland invading the CVC in a dog showing acute hypertensive encephalopathy.

Adrenal tumours are common in dogs and may secrete an excessive amount of one or more type of hormones, causing tumour-related syndromes [8,9]. They may originate in the cortex (adenoma, adenocarcinoma, and metastatic neoplasia) or medulla (pheochromocytoma, neuroblastoma, ganglioblastoma and myelolipoma) [10]. In dogs, pheochromocytomas (PPCs) account for approximately 0.01–0.1% of all canine tumours [11] and affect middle-aged to older animals with no apparent sex or breed predilection [4]. They

are usually solitary, slow-growing tumours that extend into the lumen of adjacent vessels, particularly the caval vena cava (CVC) [4,12,13].

In dogs, PCCs should be considered malignant, due to the high incidence of neoplastic invasion into surrounding tissues (up to 56% of cases [4,11,14,15] and the metastatic behaviour (regional lymph nodes, liver, spleen, pancreas, lung, heart, central nervous system, kidney and bone) [3,4].

The clinical signs associated with canine PCC are vague, non-specific, intermittent, and depending on the functional status of the neoplasia, the excessive secretion of catecholamines, the space-occupying nature of the tumour and the local invasion. Most of the associated clinical manifestations can be explained on the basis of the pharmacologic effects of catecholamines resulting in hypertension [16]. They include, but are not limited to, polyuria, polydipsia, weakness, exercise intolerance, lethargy, respiratory signs (panting, dyspnoea, coughing), episodic collapse, anorexia, weight loss, vomiting, anxiety, tremors, restlessness, irritability, depression, neurologic signs, retinal haemorrhage, retinal detachment, epistaxis, pulse deficits, systolic murmur, and arrhytmias [3,4]. Among arrhythmias, premature supraventricular and ventricular complexes and tachycardia are the most common. The conduction disturbances are due to myocardial damage, ischaemia, and fibrosis, which are a result of prolonged exposure to catecholamines from the PCC [17,18]. Some patients may present acute signs associated with a hypertensive crisis (shock, pulmonary oedema, ventricular fibrillation, or cerebral haemorrhage) [16].

Our patient was presented for an acute onset of severe neurological signs due to hypertensive encephalopathy in absence of cerebral haemorrhage. This report highlight that PCC should be included also in the differential diagnosis of dogs presented in emergency with acute central neurological disorders.

The pattern of secretion of PCCs can be persistent but more often is paroxysmal [2]. The pharmacologic effects of the catecholamines and the subsequent hypertension produced can be episodic. In fact, arterial hypertension has been documented in about 50% of affected patients during clinical examination [4]. Subsequently, a normotensive state during physical examination does not rule out the disease [4].

The concurrent presence of PCCs with other pathological conditions (e.g. diabetes mellitus, hyperadrenocorticism, hepatic disease, renal disease, and other neoplasms) has often been reported [2,5]. Hematologic, and biochemical abnormalities are usually aspecific in a patient with PCC and can derive from organs damage resulting from the hypertensive state. Thus, ante-mortem diagnosis is extremely challenging, requires a high index of suspicion and it is often achieved postmortem.

In our clinical case, ambiguous clinical signs (PU/PD, weight loss) and systemic hypertension were reported in the past year history and were interpreted as consequences of CKD. Anyway, it's not possible to exclude the possibility that a non-manifest PCC was already present and that kidneys' damage resulted from the hypertensive state and not vice-versa.

In the recent years a biochemical diagnosis of PCC in dogs has become possible. It is based on the measurement of plasma and urinary catecholamines, in particular their metabolites: metanephrines (MTNs) such as free normetanephrine (NMN), and metanephrine (MN) [12,19-23]. Recently, in human medicine, measurement of salivary MTNs has been shown to be a promising tool in the biochemical diagnosis of PCC [24] as well as a high value of urinary vanillylmandelic acid (VMA) [22]. In veterinary medicine, van den Berg et al., (2022), have tried to determine reference intervals for plasma, urinary and salivary free MTNs, NMN and 3-methoxytyramine (3MT) in a large population of healthy dogs. They also have assessed an upper reference limit (URL) for plasma free NMN (3.56 nmol/L) which has showed good diagnostic performance in detecting PCC with high sensitivity and specificity [19].

Differently, measurement of plasma and urine catecholamine concentrations showed poor diagnostic sensitivity and specificity for identifying PCC [23,25]. Although PCC should stimulate hight circulating catecholamine concentration in patient blood or urine, levels may be normal because of their variable secretion. Furthermore, high levels of stress, excitement or concurrent disease can falsely alter the catecholamine concentration in healthy patients [2]. Differently, because of their continuous neoplastic production and secretion, MTNs have higher diagnostic accuracy [26]. In fact, free MTNs are catecholamines metabolites that enter the blood stream once they have formed. In patients with PCCs, they derived almost entirely from catecholamine metabolism within the tumour. This process happens regardless the variable secretion of catecholamines and the quantity of free MTNs produced (and subsequently present in the blood stream) is proportional to the chromaffin cell mass, and therefore it is proportional to the neoplastic invasion [26,27] without sympathetic catecholamine release influence [12].

Currently, there is no consensus about the use of plasma or urine, but a strong preference for NMN determination [21]; in fact, either urine or plasma free NMN concentration showed high sensitivity and specificity for diagnosis of PCC, whereas free MN concentration showed moderate sensitivity and high specificity [12]. Furthermore the urinary and plasma free NMN have shown superiority in differentiating between PCC, hypercortisolism (HC), and nonadrenal disease [21]. It has to be remembered that discern between PCC and HC could be challenging in clinical practice, since adrenal medulla or cortex tumour cannot be distinguished ultrasonographical and many clinical signs of PCC and HC overlap.

In our case we did not need biochemical diagnosis because the evidences were enough to put PCC at the top of the differential diagnosis (constant systemic hypertension, adrenal mass with caval invasion, negative cranic TC).

In our case, ultrasound was a basic and immediate mean to address to the final diagnosis documenting an adrenal mass invading the CVC. Furthermore, a severe hypertensive cardiopathy was documented at echocolordoppler further supporting the suspected diagnosis. In our case CEUS and/or FNA sampling were not performed. Due to the presence of caval invasion, malignancy was immediately suspected, and a CT evaluation was preferred. Once the CVC invasion was also confirmed by CT, a surgical approach was planned.

Ultrasound imaging is a rapid, non-invasive, and reliable modality to evaluate suspected adrenal lesions. An adrenal mass can be detected by ultrasonography in 50% to 83% of cases of canine PCC [2,3,5], but failing at visualising it does not rule out a possible PCC diagnosis. Although not pathognomonic, structural features (i.e., lesion shape, size, and echotexture) are often useful diagnostic criteria. Large masses or nodules ≥ 2 cm strongly suggest malignant adrenal gland neoplasia [28,29]. At ultrasound examination, PCC can appear as a large, irregular, amorphous, encapsulated mass, associated with loss of shape and parenchymal structure. Mixed echogenicity, due to the presence of haemorrhagic/necrotic areas, is also characteristics. Most PCC are unilateral (only 10% are bilateral) [15,30], and the contralateral adrenal gland is of normal size and shape. PCCs in dogs are more likely to be aggressive and vascular invasion and metastases are commonly reported, respectively in up to 85% and 40% dogs [4,5,28,29,31]. Tumour thrombus may extend into the phrenicoabdominal vein and caudal vena cava [29].

Even though the contrast-enhanced ultrasound (CEUS) examination of adrenal lesions is poorly reported in veterinary literature, CEUS imaging can be a valuable tool in order to assess the malignancy of an adrenal lesions. Few studies describe the features of PCC during CEUS examination [32,34]. PCC seems to be characterized by a fast wash-in followed by a seemingly fast wash-out and shows both hypo perfused areas and intralesional microcirculation, as a probable result from the presence of haemorrhagic and necrotic areas and tumour neo-angiogenesis [33]. CEUS can also potentially differentiate PCC from other adrenal condition (i.e. adenocarcinoma, cortical adenoma); PCC, in fact, has a

significantly lower mean transit time compared to both adenocarcinoma and cortical adenoma [32-34]. However, cytology and histology are necessary to obtain the final diagnosis.

Computed tomography imaging (CT) has now become a routinary examination for preoperative assessment of dogs with adrenal mass. It is considered more accurate than ultrasonography for the assessment of vascular invasion [35]. When a PCC is suspected, a CT scanning is the gold standard and a prerequisite before a surgery is planned; it allows to conduct a screening for possible metastasis (including lymph nodes, liver, lungs, kidney, spleen, and bone) [3], and assessing the vascular invasion influence the surgical approach for the tumour resection [15]. The histologic composition of adrenal neoplasms is heterogeneous in both humans and dogs with variable amounts of haemorrhage, necrosis and/or mineralization occurring in benign and malignant neoplasms [36]. Therefore, different neoplasm, such as PCC, adenocarcinoma, or adenoma, may appear similar in CT images [37,38].

PCC, like other neuroendocrine tumours, has a typical cytologic features: naked uniform nuclei, typical disposition of nuclei in rows and rosette-like structures, fine chromatin with inconsistent nucleoli [39].

Cytology can be an immediate, minimally invasive method to discern the origin of a primary adrenal mass (as PCC). In fact, can be a useful tool in discerning a cortical tumour from a medullary one, since discerning the two of them can be challenging if only sustained by clinical, diagnostic imaging and laboratory findings. In dogs, fine needle aspiration can be performed percutaneously under ultrasound guidance, as minimally invasive procedure. Even though, risk of complications (bleeding, hematic contamination, neoplastic spreading along the needle path) discourages veterinarians from performing adrenal cytologic samples, in veterinary medicine, risk assessment is only anecdotal. Evidence is based on few reports in human literature [40-43], in which are reported complications after PCC aspiration (fatal haemorrhage, hypertensive crisis or paradoxical hypertensive and hypotensive crises). Some studies [39,44] suggest that, in optimal conditions, fine needle aspiration (FNA) of adrenal lesion can be considered a minimally risky procedure. Pey et al.,2020, in their study, report that the complications rate was similar to what has recently been published about FNAs of the adrenal lesions and comparable to the complication rate of FNAs of other abdominal organs. Although for the majority of adrenal tumours the resolution is surgical, cytological examination allows the clinician to advance a more accurate diagnostic suspicion of PCC and to implement pre-operative pharmacological therapies before surgical procedures.

The definitive diagnosis of PCC relies on histopathology of the adrenal mass [12,13]. Histological PCC appearance can vary. Usually, they present a typical morphology, characterized by polygonal cells with round to oval nuclei and prominent nucleoli, granular cytoplasm arranged in small nest, separated by fibrovascular stroma. Tumour cells are often subdivided into small lobules by connective tissue septa and capillaries, creating a papillary pattern [30]. However, morphology can be atypical. In these cases, immunohistochemistry pays an important role in confirming diagnosis [45].

Pharmacological therapy is not recommended except in the case of inoperable or metastatic PCCs. It consists in administration of alfa-blocker (phenoxybenzamine or prazosin). Calcium channel blockers may be of use in controlling hypertension, due to their blocking action on synaptic calcium channel and direct vasodilatory effects [2].

Also, since preoperative administration of an alpha-blocker (phenoxybenzamine or prazosin) has reduced mortality in human patients [46,47] and, previous studies have showed a significant decrease in perioperative mortality in dogs when preoperative alpha-blocker therapy was given; pharmacological treatment with alpha-blockers is recommended before surgery [1,13]. A low dose should be used initially with gradual increase to achieve normotension. Beta-blocking agents may be used to control arrhythmias or tachycardia but should never be used without concurrent alpha-blockade to avoid a state of severe hypertension with loss of the vasodilatory effects [2].

In our dog supportive pharmacological therapy was immediately started to reduce systemic pressure with the aim to contrast hypertensive encephalopathy and stabilize the patient as much as possible until surgery decisions were taken. The emergency protocol included labetalol, a combined alpha- and beta-adrenoceptor blocking agent that was used off label with some positive results in the first 72hours of monitoring. Despite the scant literature in terms of dosage and effects in dogs, we choose to continue with the alpha blocker prazosin at 1 mg. The drug is more commonly used for urinary tract obstruction in cats.

Adrenalectomy is the treatment of choice for PCC. Surgical resection of invasive PCC can be technically demanding [2,5] but in absence of local invasion, it can often be completely resected [16]. Nonresectable tumours should be debulked as much as possible to reduce the circulating catecholamine concentrations and improve the efficacy of pharmacological management [2]. Potential risk factors associated with poor short-term survival time in dogs undergoing adrenalectomy include size, tumour type, additional surgical procedures performed in the same anaesthetic event, metastasis, and acute adrenal haemorrhage [14, 48-50].

After a resection of a functional PCC, postoperative mortality can be influenced by the patient's response to a sudden removal of the source of catecholamine release [51]. When the tumour is excised, the decrease in circulating catecholamines may lead to pronounced hypotension [2], sometimes it can be considered refractory hypotension, a postoperative complication with (or without) systemic consequences [51]. If blood pressure does not to decline after the surgical adrenal removal, unidentified metastases are likely to be present [2,5,16].

Short-term mortality rates after adrenalectomy have decrease in the last few years, as Enright et al, 2022, show in their study. They assess a short-term surgical success rate with 44/53 dogs (83%) surviving to discharge from the hospital [51].

Unfortunately, our patient's clinical conditions abruptly deteriorated before surgery was performed. Histology examination confirmed a PCC of right adrenal gland, invading the CVC.

5. Conclusions

This report describe a dog developing acute hypertensive encephalopathy due to PCC and highlight that PCC should be included in the differential diagnosis of dogs presented in emergency with acute central neurological disorders.

Ultrasound is a useful and immediate test that should be included in the diagnostic protocol of dogs with acute onset of neurological signs with or without documented hypertension. In fact a normotensive state during physical examination does not rule out the disease. Also, echocardiographic features of hypertensive cardiopathy could help to address the diagnosis even in absence of registered hypertension.

Despite the final exitus of this specific case, pharmacological therapy seems to be able to reduce systemic pressure with initial improvement of clinical conditions.

Early diagnosis is particularly relevant in view of a resolutive surgical approach. Veterinarians need to be aware that comorbidities (i.e. CKD) could mask clinical signs and delate the diagnosis.

6. Conflicts of interest

The authors declare no conflict of interest.

7. Author Contribution

A.R. and P.P. conceptualised, wrote and supervised the article. B.G., S.D., A.C provided her expertise on clinical and biochemical aspects. All authors have read and agreed to the published version of the manuscript.

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9. Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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