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CASE REPORT

Diagnosis, treatment and outcome of pheochromocytoma in a cat

M. T. Prego*, M. J. Dias*†‡, L. Mestrinho *†‡, R. Englar§, G. Grinwis¶, S. Galac ** and R. O. Leal *†‡,1

* Veterinary Teaching Hospital/Faculty of Veterinary Medicine, University of de Lisbon, Lisbon, Portugal
† CIISA – Centre for Interdisciplinary Research in Animal Health - Faculty of Veterinary Medicine, University of Lisbon, Lisbon, Portugal
‡ Associate Laboratory for Animal and Veterinary Sciences (AL4AnimalS), University of Trás-os-Montes and Alto Douro, Vila Real, Portugal
§ College of Veterinary Medicine, University of Arizona, 1580 E Hanley Blvd, Oro Valley, Arizona 85737, USA
¶ Veterinair Pathologisch Diagnostisch Centrum - Department of Biomolecular Health Sciences, Utrecht University, Utrecht, The Netherlands
** Department of Clinical Sciences, Utrecht University, Utrecht, The Netherlands

[1]Corresponding author email: rleal@fmv.ulisboa.pt

Pheochromocytoma in cats is a rare clinical condition characterised by the development of a secretory endocrine tumour that arises from the adrenal medulla. An 8-year-old castrated male, domestic shorthair cat was referred for further investigation of a 4-month history of progressive weight loss with normal appetite, polyuria/polydipsia, generalised weakness, and severe hypertension. Sonography and computed tomography of the abdomen disclosed a mass arising from the left adrenal gland. The contralateral adrenal gland was normal in size and shape. Results from a low dose dexamethasone suppression test and measurements of plasma aldosterone concentration and plasma renin activity ruled out a cortisol-secreting tumour and aldosteronoma. The clinical presentation made a sex-steroid secreting tumour unlikely. Increased plasma metanephrine and normetanephrine concentrations prioritised the differential diagnosis of pheochromocytoma. The cat underwent adrenalectomy of the left gland and histopathological diagnosis with immunohistochemical markers confirmed the diagnosis.

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INTRODUCTION

Adrenal neoplasia is an uncommon clinical occurrence in cats, accounting for 0.2% of all feline neoplasms (Lunn & Boston 2020). Pheochromocytoma (PCC) is a catecholamine-producing neuroendocrine tumour arising from chromaffin cells of the adrenal medulla (Galac 2017). While it is uncommonly diagnosed in dogs, PCC is clinically rare in cats, and has been described by few case reports (Henry *et al.* 1993, Chun *et al.* 1997, Wimpole *et al.* 2009, Calsyn *et al.* 2014, Daniel *et al.* 2016, Cervone 2017). To date, no published study details the comprehensive diagnostic approach to PCC in a cat, including the measurement of plasma metanephrines and concurrent histopathology and immunohistochemistry.

CASE HISTORY

An 8-year-old castrated male, domestic shorthair cat was presented to the referring veterinarian (rDVM) for evaluation of a 4-month history of progressive weight loss despite an unchanged appetite, polyuria/polydipsia, and generalised weakness. The patient had been adopted into a multi-cat household as a stray 4 years previously. Aside from undergoing full-mouth extractions 1 month after adoption due to caliciviral-associated chronic gingivostomatitis, the cat had no past pertinent health concerns. Retroviral status was negative with respect to feline leukaemia and feline immunodeficiency viruses.

Physical examination by the rDVM was unremarkable other than that the cat appeared lethargic. Systolic blood pressure

(SBP) measured by oscillometry was consistently elevated at 180 to 200 mmHg. The rDVM advised that an abdominal ultrasound be performed. The study disclosed a heterogeneous nodular structure caudal to the celiac and cranial mesenteric arteries. Based upon location, the mass was presumed to originate from the left adrenal gland (Fig 1).

The cat was referred to the Internal Medicine Service of the Faculty of Veterinary Medicine - University of Lisbon, to complete the diagnostic work-up of the adrenal mass. Mass location was confirmed by abdominal computed tomography (CT), which identified a 17-mm diameter tumour arising from the left adrenal gland. There was no evidence of vascular invasion; however, the mass appeared to be attached to the caudal vena cava, deflecting it ventrally (Fig 2). The contralateral adrenal gland was normal in size and structure. Thoracic CT was performed at the same time as the abdominal scan and detected an increased lung density with focal peribronchovascular distribution in the right cranial lobe. The origin of this lesion was suspected to be inflammatory or infectious. Neoplastic origin was deemed less likely. Fine-needle aspiration was advised as a means of further investigation, but was declined by the client.

On presentation, the cat was lethargic, underweight (3.3 kg) with a body condition score of 2/9, and hypertensive (SBP of ±200 mmHg; oscillometry). A grade III/VI holosystolic heart murmur was present on thoracic auscultation. The remainder of the physical examination was within normal limits. Blood was drawn and submitted for complete blood count (CBC) and serum biochemistry analysis, which included a thyroid panel. Clinicopathologic abnormalities included mild elevated creatinine (2.5 mg/dL) and hyperkalemia (6 mmol/L). Urinalysis disclosed a urine specific gravity of 1.021. Amlodipine (0.625 mg per os every 24 hours) was initiated to medically manage systemic hypertension.

In order to determine if the adrenal tumour was functional and to predict its most likely origin, an endocrine investigation was conducted. A low dose dexamethasone suppression test (LDDST) was performed and demonstrated an appropriate negative feedback response to exogenous dexamethasone administration (0.1 mg/kg intravenously): cortisol concentrations (chemiluminescence; Immulite 1000; Siemens) were both less than 1 µg/dL at 4 and 8 hours after injection. Hypercortisolism secondary to a functional cortisol-secreting tumour was therefore considered unlikely. An aldosteronoma was also deemed unlikely based upon measured plasma aldosterone (151.62 pg/mL; reference range: 15 to 102) and plasma renin activity (PRA) (0.86 ng/mL/hour; reference range: 0.4 to 1.9) [radioimmunoassay; IDEXX Laboratories], an aldosterone: renin ratio of 2.44 (reference range: 0.3 to 3.8; Javadi *et al*. 2004), and a serum potassium concentration of 6 mmol/L.

As the next step in the diagnostic work-up, plasma metanephrine (PL-MN) and normetanephrine (PL-NMN) were measured using high performance liquid chromatography (HPLC; IDEXX Laboratories). Measurements of PL-MN and PL-NMN were, respectively, 4.60 and 54.87 nmol/L. Although reference ranges for PL-MN and PL-NMN in cats have yet to be established, the patient's results were 4.2 and 15.6 times higher than the mean values previously reported in healthy cats by HPLC, set

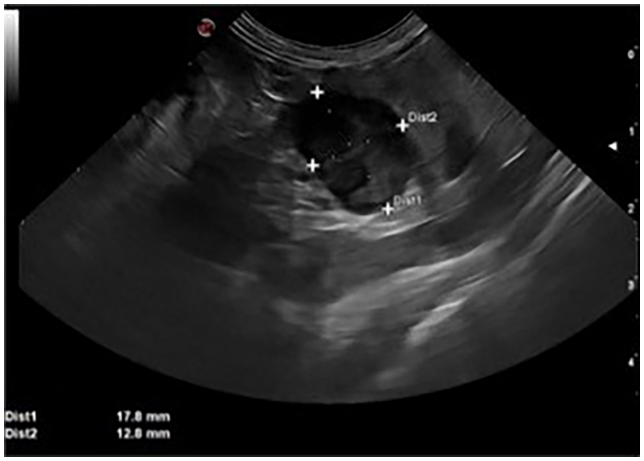

FIG 1. Abdominal ultrasound showing a heterogeneous nodular structure suspected of having its origin in the left adrenal gland (original)

as 1.1 nmol/L (range: 0.25 to 3.3) and 3.5 nmol/L (range: 1.16 to 6.28), respectively (Wimpole *et al*. 2009).

Treatment with phenoxybenzamine (PBZ) was initiated (2.5 mg po every 12 hours) and the cat submitted to weekly weight and SBP measurements, as well as biweekly serum creatinine and potassium measurements. PBZ was well tolerated, with no reported side effects. Two weeks after initiating PBZ, amlodipine was discontinued following an at-home episode of acute weakness, despite normal SBP at consultation (140 to 150 mmHg). Eight weeks later, SBP (±150 mmHg), serum creatinine (1.7 mg/dL) and serum potassium (5.6 mmol/L) levels were stable, allowing planning to move forward for a left adrenalectomy. Pre-surgical echocardiography was unremarkable. Pre-surgical thoracic and abdominal CT were recommended but the client declined due to financial constraints. In lieu of CT, abdominal sonography and thoracic radiography were performed. Thoracic radiographs were unremarkable. Abdominal ultrasound revealed that the adrenal lesion was stable in size, without apparent vascular invasion, despite neighbouring the caudal vena cava wall.

The last dose of PBZ was administered by mouth the evening before surgery. Laparotomy allowed access to the adrenal mass. Because of the extent to which the mass had adhered to the wall of the caudal vena cava (Fig 3), adrenalectomy with a partial cavectomy was performed. Towards the end of the procedure, when the vena cava was partially occluded, the patient experienced transient hypotension. Apart from this transient episode, there were no additional intraoperative complications. Blood pressure and serum creatinine levels were monitored every 12 and 24 hours, respectively. The immediate postoperative period was uneventful, and the patient was discharged 48 hours after surgery.

The adrenal mass, homogeneously light brown in colour, solid in consistency, measuring 1.5×1.7×1.4 cm in size and preserved in formol, was submitted for histopathology and immunohistochemistry for medullary markers chromogranin A and synaptophysin, at the Veterinary Pathology Diagnostic Center, Faculty of Veterinary Medicine, Utrecht University. Histopathological

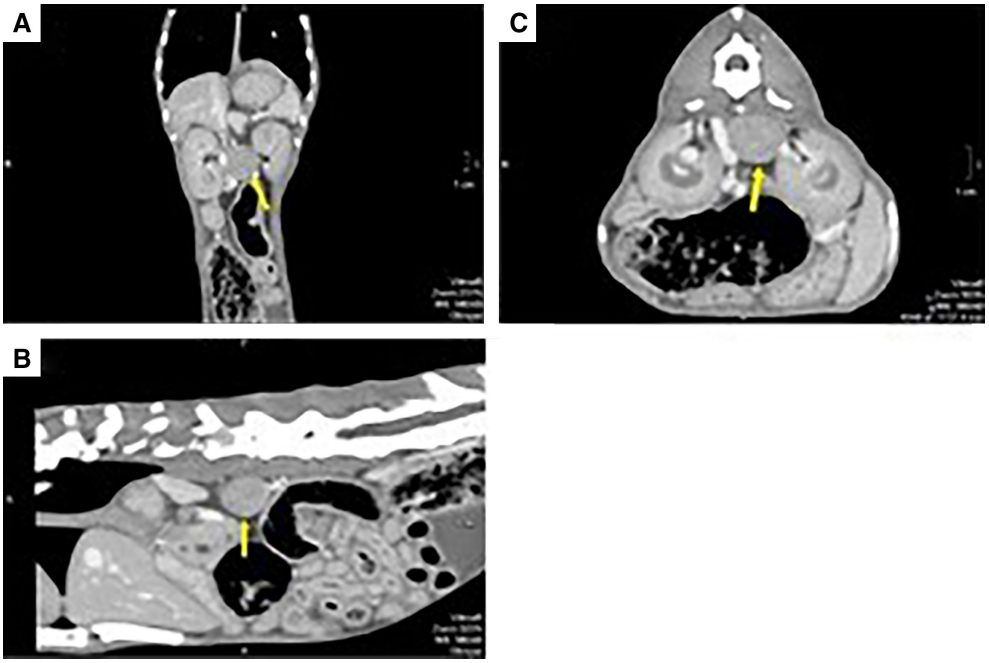

FIG 2. Abdominal computed tomography showing a 17-mm diameter mass arising from the left adrenal gland (original). (A) Coronal plane; (B) sagittal plane; (C) axial plane

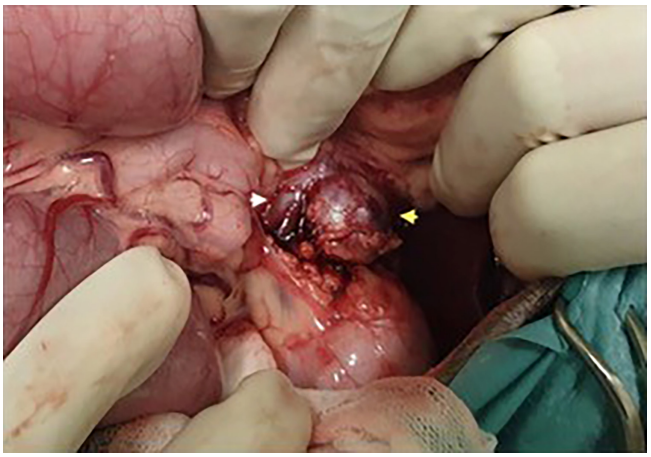

FIG 3. Intraoperative image of the adrenal mass (yellow arrow) and the caudal vena cava (white arrow) partially compressed by the surgeon's hands (original)

analysis revealed the presence of a narrow band of cortical tissue with extracapsular foci of hyperplasia. The adrenal gland consisted mainly of trabeculae of neoplastic cells and fibrovascular septa that contained palisade neoplastic cells. Neoplastic cells were characterised as having several, large, elongated oval nuclei within a scant amount of amphophilic cytoplasm (Fig 4). Mitotic index was low. Many neoplastic cells stained positive for both synaptophysin and chromogranin A (Fig 5). These results were confirmatory for PCC.

The cat recovered well at home and its generalised weakness resolved. Transient hyporexia was reported by the owner. Some degree of polyuria/polydipsia remained present. Blood pressure was reassessed weekly after surgery for a duration of 5 weeks. Values were persistently normotensive. Thereafter, evaluation was extended to once every 2 months.

Two months after surgery, serum creatinine was reassessed (creatinine: 2.32 mg/dL). A diagnosis of International Renal Interest Society stage II, non-hypertensive, non-proteinuric chronic kidney disease (CKD) was made. Seven months after surgery, the cat re-presented on emergency for acute prostration, noisy breathing, and sneezing. Clinical examination disclosed an absence of the left pupillary light reflex, unilateral (left-sided) exophthalmos (reportedly present for 48 hours), oral ulceration, cachexia, and an estimated 5% dehydration. Prioritised differential diagnoses included inflammatory orbital disease, zygomatic salivary gland disease, neoplasia of the orbit or other surrounding tissues and PCC metastases in the central nervous system. Because prior thoracic CT had identified a pulmonary lesion that was lost to follow-up, other hypotheses such as PCC lung metastasis or bronchoalveolar carcinoma could not be ruled out. CBC and serum biochemistry profiles were repeated and revealed persistent but stable azotemia. The client declined cranial and thoracic CT and elected for humane euthanasia. The patient's survival time after the diagnosis of PCC and adrenalectomy was 9 and 7 months, respectively.

DISCUSSION

This case report describes a PCC in a cat in which an adrenal mass was detected concurrent with severe hypertension. Based on a literature review, this is the first case report to include both biochemical and histopathological diagnosis of a PCC in a feline patient. In addition, this case report outlines the step-by-step diagnostic approach that constitutes a comprehensive investigation of an adrenal mass in a cat.

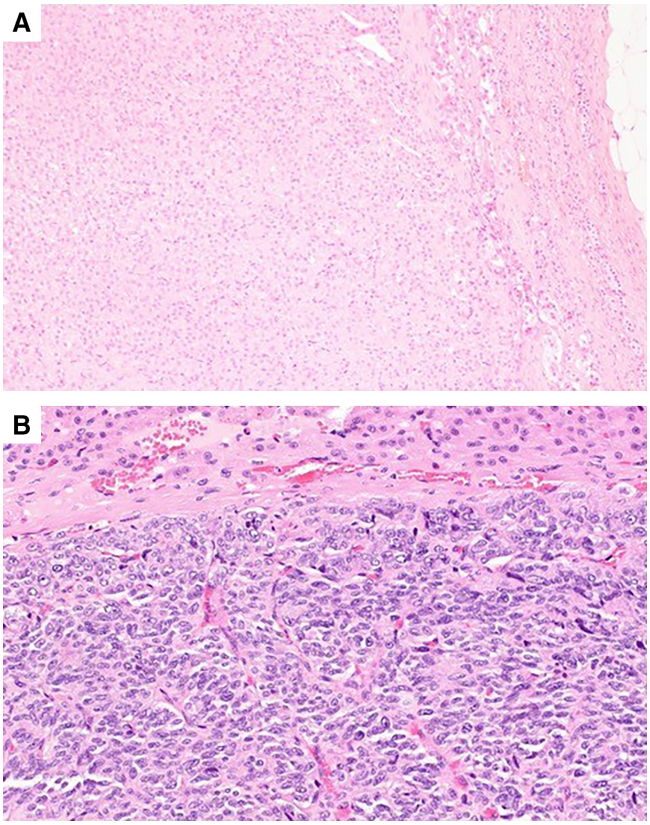

FIG 4. Photomicrographs of the left adrenal gland (haematoxylin–eosin stain) (original). (A) Narrow band of normal cortical tissue compressed by the neoplastic tissue with pheochromocytoma histopathological features (×10); (B) trabeculae of neoplastic cells with several, large, oval nuclei within a scant amount of amphophilic cytoplasm (×20)

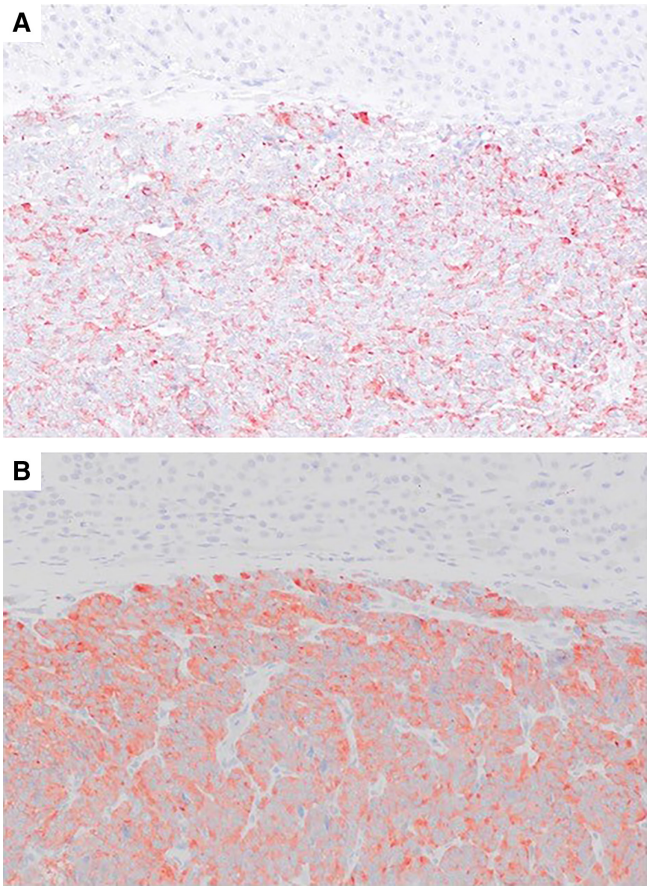

FIG 5. Immunohistochemistry of the left adrenal gland (original). (A) Chromogranin A (×10); (B) synaptophysin (×10). (A, B) Many neoplastic cells stained positive for both medullary markers

Not including this case report, only six cats with histologically confirmed PCC appeared in the veterinary medical literature (Henry *et al*. 1993, Chun *et al*. 1997, Calsyn *et al*. 2014, Daniel *et al*. 2016). In addition, two cats with suspected PCC, but without histopathological confirmation, have been described (Wimpole *et al*. 2009, Cervone 2017). Immunohistochemistry with adrenomedullary markers chromogranin A and synaptophysin has previously been applied to the diagnostic intervention of only one other case, in which an adrenocortical adenoma was diagnosed in one gland and a PCC in the contralateral gland (Calsyn *et al*. 2014). Previous case reports of feline PCC, described polyuria/polydipsia and systemic hypertension in three of eight cats and in two of eight cats, respectively (Melián & Pérez-López 2019). The cat in this case report exhibited both clinical conditions.

The primary differential diagnoses of an adrenal mass with concurrent hypertension in a feline patient include functional cortical tumours (aldosteronoma and hypercortisolism), PCC, and non-secretory adrenal tumours with a concurrent disease such as acromegaly, hyperthyroidism and/or CKD (Galac 2017, Melián & Pérez-López 2019). The LDDST is considered the test of choice for the diagnosis of hypercortisolism in cats due to its high sensitivity and moderate specificity (Chiaramonte & Greco 2007, Boland & Barrs 2017). Our patient's appropriate negative feedback response to exogenous glucocorticoid administration ruled out hypercortisolism. Serum aldosterone measurement is the diagnostic hallmark of feline primary hyperaldosteronism. It is the test of choice for hypokalemic patients with systemic hypertension and should be interpreted in combination with serum potassium concentration and PRA assessment (Schulman 2010). The cat in this case report demonstrated borderline high serum potassium concentration, a slight increase in serum aldosterone levels, and PRA and aldosterone: renin ratio values within the reference range. This constellation of lab results made aldosteronoma unlikely, as the authors would have expected a minimal PRA and concurrent hypokalemia in case of autonomous secretion of aldosterone by the adrenal gland. Adrenocortical tumours have the capacity to synthesise and secrete steroid hormones other than cortisol and aldosterone, including androgens, estrogens and progestogene (Reusch 2015, Melián & Pérez-López 2019). Cats that produce excessive sex hormones may exhibit clinical signs such as poor haircoat, dermal atrophy and skin fragility, or changes in the genitalia, urine odour and sexual behaviour, depending on the sex hormone that is being excessively secreted (Behrend 2017). Given that the clinical signs observed in this cat were not consistent with those reported in cats with excessive sex hormones secretion, endocrine testing for sex hormones was not indicated (Rossmeisl *et al*. 2000, Boag *et al*. 2004, Millard *et al*. 2009).

Initial screening for PCC should include the assessment of fractionated metanephrines in urine and/or plasma (Galac & Korpershoek 2017). In cats, there are only two published studies concerning these biomarkers (Wimpole *et al*. 2009, Sasaki *et al*. 2021), one of which established guidance with respect to reference ranges for PL-MN and PL-NMN in healthy cats as measured by HPLC. According to this study, PL-MN (4.60 nmol/L) and PL-NMN (54.87 nmol/L) measurements in our patient were compatible with the diagnosis of PCC (Wimpole *et al*. 2009). Because there were no signs of vascular invasion nor evidence of distant metastatic disease, a left adrenalectomy was performed. Although there is currently no data supporting the use of PBZ in cats to minimise the deleterious effects of excessive catecholamine secretion, perioperative mortality has been shown to be significantly lower in dogs pretreated with PBZ compared to untreated dogs (Herrera *et al*. 2008). For this reason, the authors initiated treatment with PBZ (2.5 mg po every 12 hours) before surgery.

In a retrospective study with three confirmed cases of feline PCC (ante-mortem or on necropsy), the median survival time was 20 weeks (Daniel *et al*. 2016). In one case, the cat was alive 36 months after surgery (Calsyn *et al*. 2014). In other case, the cat developed fatal thromboembolic disease postoperatively and was euthanased (Chun *et al*. 1997). This patient's survival time after the biochemical diagnosis of PCC and adrenalectomy was 36 weeks (9 months) and 28 weeks (7 months), respectively. The owner elected for euthanasia when the patient was presented with prostration, noisy breathing, left exophthalmos, absence of the left pupillary reflex, cachexia and dehydration. Among the differentials considered, PCC metastatic disease in the central nervous system was hypothesised, as it has already been described in humans and dogs (Galac & Korpershoek 2017). Despite the fact it was not monitored with follow-up CT, this patient's pulmonary lesion may have also contributed to the observed progression of this clinical case. Although a neoplastic origin initially appeared to be unlikely, a bronchoalveolar carcinoma or a lung PCC metastasis could not be definitively ruled out. Approximately 50% of cats with PCC described in the literature have concurrent neoplasia (Melián & Pérez-López 2019). This raises the concern of a potential association between this cat's isolated pulmonary lesion and PCC. Moreover, there is an isolated case in the literature documenting bronchoalveolar carcinoma in a cat with a suspected PCC (Wimpole *et al*. 2009). Lung tumours in cats have a history of metastasizing to the digits as well as other locations, including muscle, eyes, the lungs and the aorta. This so-called MODAL syndrome that has been associated with metastatic pulmonary carcinoma in cats is possible in this patient, particularly given the cat's progression to ocular signs (Thrift *et al*. 2017).

Because additional diagnostic tests were declined per owners, a definitive diagnosis of the condition that precipitated euthanasia is unknown.

This is a case report of a feline PCC confirmed by standard histopathology and immunohistochemistry for medullary markers chromogranin A and synaptophysin. This case report highlights that, albeit rare, PCC should be included among the differential diagnoses that are considered for adrenal masses in feline patients. Because presenting signs are often non-specific, clinical awareness represents a crucial initial step in the diagnosis of PCC.

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Author contributions

M. T. Prego: Methodology (equal); visualization (equal); writing – original draft (equal). **M. J. Dias:** Investigation (equal); visualization (equal); writing – original draft (equal). **L. Mestrinho:** Methodology (equal); resources (equal); supervision (equal); validation (equal). **R. Englar:** Validation (equal); writing – review and editing (equal). **G. Grinwis:** Investigation (equal); methodology (equal); resources (equal); validation (equal). **S. Galac:** Conceptualization (equal); data curation (equal); funding acquisition (equal); investigation (equal); methodology (equal); resources (equal); supervision (equal); visualization (equal); writing – review and editing (equal). **R. O. Leal:** Conceptualization (lead); formal analysis (lead); investigation (lead); methodology (lead); project administration (lead); supervision (equal); validation (equal); visualization (equal); writing – review and editing (lead).

Conflict of interest

None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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