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CASE REPORT
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Pituitary Carcinoma in a Bitch: Clinical, Tomographic, Histopathological and Immunohistochemistry Findings

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ABSTRACT

***Background*:** Primary pituitary carcinoma is rarely reported in dogs and only few reports describe its malignancy. In veterinary literature, primary pituitary carcinomas correspond up to 2.4% to 3.4% of intracranial neoplasms found in dogs and information regarding its biological behavior is quite limited. In humans, primary pituitary carcinomas represent less than 1.0% of all tumors found in the pituitary gland. The proposed classification for pituitary carcinoma in humans and dogs determines that the tumor must have its origin in adenohypophyseal region and disseminated metastasis by cerebrospinal fluid or systemically to other organs must be observed. In dogs, a few reports have described primary pituitary carcinoma. The goal of this report was to describe clinical, tomographic, histopathological and immunohistochemistry features of a bitch with primary pituitary carcinoma with adjacent invasion.

***Case*:** A 7-year-old female spayed Golden Retriever dog was assessed by general practice due progressive weight loss, muscular atrophy, lethargy, blindness, head pressing, and hyporexia for 21 days. Computed tomography (CT) showed a cerebral parenchyma with expansive extra-axial base formation, originating from sella turcica topography, measuring about 2.0 cm dorsally, displacing the third ventricle, suggesting the diagnosis of pituitary neoplasia. The hormones thyroid-stimulating hormone (TSH) and total thyroxine (T4) as well as stimulation ACTH test were unremarkable. After 7 days, neurological clinical signs progressed and unfortunately the patient died ten days later after hospitalization. A necropsy exam revealed pituitary gland with increased dimensions (2.5 x 2.0 cm). Histopathological findings revealed tumor proliferation in pituitary gland. The neoplasm showed invasion to the nervous parenchyma and metastatic foci between the brain lobes. Immunohistochemistry was positive for keratin and neuron-specific enolase and negative for epithelial membrane antigen, S-100 protein, glial fibrillary acidic protein, estrogen receptor, CD34, chromogranin, somatostatin, and ACTH. The clinical, histopathological and immunohistochemistry findings supported the diagnosis of primary pituitary carcinoma.

***Discussion*:** There is lack information regarding pituitary carcinoma prevalence in dogs, and little is known about its pathological and clinical features. The patient showed a shorter survival time (30 days after the onset of clinical signs) for a non-hormonally functional tumor that presented with acute onset of neurological signs due to local effect of an expanding mass, also described in others pituitary carcinoma reports. It was observed a metastatic focus of pituitary neoplasia between cerebral hemispheres, leading us to conclude to be a pituitary carcinoma. Adjacent infiltration was noticed by the presence of neoplasm invasion to the synoptic nervous parenchyma and metastatic foci between the brain lobes as well as the presence of a non-delimited nodular area of neoplastic implantation between the cerebral hemispheres, and optic nerve compromised by neoplasm cells. The data reported here showed that a negative ACTH receptor in neoplasm with 10% Ki-67 proliferation index with no history of clinical signs of pituitary-dependent hyperadrenocorticism (PDH). Pituitary adenocarcinomas are thought to be more often non-secretors. CT findings reveled a pituitary mass of 2.5 cm in vertical height suggesting a pituitary macrotumor although there is lack of description for pituitary carcinomas in veterinary literature. The animal had a fast deterioration of his clinical condition and quickly came to death, suggesting poor biological behavior of the tumor.

Keywords: adrenocorticotropic hormone, case report, dog, pituitary tumors.

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INTRODUCTION

Primary and metastatic pituitary tumors correspond to 24.0% of all intracranial neoplasms in dogs [14,22]. Among primary pituitary tumors, adenomas are the most diagnosed ranging from 13.6 to 21.4% [7,14,22]. In dogs, adrenocorticotrophic hormone (ACTH) produced by corticotroph pituitary adenomas are the most common diagnosis and generally originate from *pars distalis*, although other adenomas can also occur from somatotrophic, lactotrophic or multi-hormonal origin [7,9,11,18].

Primary pituitary carcinomas in dogs are rare, and information regarding its biological behavior is quite limited. According to literature, primary pituitary carcinomas account for 2.4% to 3.4% [14,22] of intracranial neoplasms found in dogs. In humans, primary pituitary carcinomas represent less than 1.0% of all tumors found in the pituitary gland [6]. According to the World Health Organization (WHO), for a pituitary tumor to be classified as a carcinoma, its origin must be adenohypophyseal and disseminated metastasis by cerebrospinal fluid or systemically to other organs must be observed [6]. In dogs, there are only few reports describing primary pituitary carcinoma [1,2,8,12,20,21]. This report describes clinical, tomographic, histopathological and immunohistochemistry features of a dog with primary pituitary carcinoma with adjacent invasion.

CASE

In order to increase the accuracy and usefulness of the case report, we followed the CARE guidelines checklist for case reports [13]. The animal was client-owned and signed written consent was obtained. A 7-year-old female spayed Golden Retriever dog was assessed by general practice due progressive weight loss, muscular atrophy, lethargy, blindness, head pressing, and hyporexia for 21 days. The patient was hospitalized in the intensive care service and received hydroelectrolytic replacement with Ringer's Lactate®[1] and enteral feeding. Due to its neurological signs, the patient was referred to computed tomography (CT).

CT images revealed a cerebral parenchyma with expansive extra-axial base formation, originating from sella turcica topography, well defined, with moderate heterogeneous hyperattenuation, measuring about 2.0 x 1.9 x 1.9 cm [height, width and length] dorsally displacing the third ventricle, with an area of perilesional hypoattenuation. These findings were highly suggestive of a pituitary macrotumor (Figure 1).

After CT results, the patient was referred to endocrinology sector. The hormones thyroid-stimulating hormone (TSH) and total thyroxine (T4) as well as stimulation adrenocorticotropic hormone (ACTH) test were performed, in which were unremarkable according to laboratory reference. After 7 days, clinical signs progressed to cachexia, muscular atrophy, absence menace response, bilateral mydriasis, circling, and head pressing. Complete blood count (CBC) showed only severe leukopenia (1,000 cells/μL, reference range: 6,000-17,000 cells/μL), and unfortunately the patient died 10 days later after hospitalization.

A necropsy exam was authorized by the owners, in which revealed blood vessels congested in the central nervous system, pituitary gland with increased dimensions (2.5 cm height x 2.0 cm width), presenting an expansive growth for the sella turcica, extra sellar, generating its enlargement, and dorsal growth for the base of the brain, compressing the vessels and nerves of the region (optic chiasm, oculomotor nerve and olfactory tract), also reaching the hypothalamus region, and compressing the third ventricle (Figure 2). No metastasis was observed in other organs in necropsy exam.

Microscopic findings revealed tumor proliferation in pituitary gland with proliferation of round cells containing cellular polymorphism, round-shaped, hyperchromatic or slightly dotted nucleus and pale pinkish cytoplasm; accentuated karyorexis and some cells with karyomegaly and multinucleation; rare figures of mitosis interspersed with fibrovascular stroma, with congested vessels and a large area of hemorrhage. The neoplasm showed invasion to the nervous parenchyma and metastatic foci between the brain lobes above the main lesion. In a brain-based region, multifocal infiltration of the pituitary neoplasia cells was observed, as well as the presence of a non-delimited nodular area of neoplastic implantation between the cerebral hemispheres (Figure 3A). The optic nerve was extensively compromised with the cells of the pituitary neoplasm, compromising the architecture of the neural fibers. These findings supported the diagnosis of primary pituitary carcinoma. In immunohistochemistry evaluation, the tumor cells were positive for keratin (AE1AE3)[2] and neuron-specific enolase (NSE)[3]. Negative staining was observed for epithelial membrane antigen (EMA)2, S-100 protein[2], glial fibrillary acidic protein (GFAP)[2], estrogen receptor[2], CD342, chromogranin[4], somatostatin[4], and ACTH4. The Ki-672 proliferation index was 10% within neoplastic cells (Figure 3 B, C, D, E & F).

DISCUSSION

According to WHO, the term pituitary carcinoma refers to a malignant pituitary neoplasia with the occurrence of local metastasis in central nervous system (CNS) or distant in other organs [6]. In veterinary medicine, it was proposed to use the same classification criteria for pituitary carcinoma [18]. In our study it was observed a metastatic focus of pituitary neoplasia between cerebral hemispheres, leading us to conclude to be a pituitary carcinoma. Other studies have described metastasis of breast, kidney, thyroid, prostatic, vesical and anal sac neoplasms in pituitary gland [22]. In this present case report, a necropsy and histopathologic studies showed no neoplasms in other organs, confirming that the tumor found was a primary pituitary neoplasia.

In humans, some pituitary carcinomas may be hormonally functional secreting adrenocorticotropic hormone (ACTH) and the patient may present clinical signs of pituitary-dependent hyperadrenocorticism (PDH) [4,15,17]. In dogs, little information is known about pathological and clinical features of pituitary carcinomas. Pituitary adenocarcinomas are thought to be more often non-secretors. However, other reports described four cases of ACTH secreting pituitary carcinomas, in which one dog presented with ACTH producing pituitary carcinoma with shorter survival times compared to those non-secretors [3,8,10]. In contrast to these authors, but according to a case reported [5] our case showed a dog with no history of PDH signs and a negative ACTH stimulating test. The animal had a fast deterioration of his clinical condition and quickly came to death, suggesting poor biological behavior of the tumor.

The dog's clinical signs such as cachexia, sarcopenia and acute onset of neurological signs were due to paraneoplastic syndrome and local effect of the expanding mass observed in necropsy exam. In literature, one report [8] also described a case of pituitary carcinoma in which the dog presented anorexia and circling. These same clinical signs were observed in others pituitary carcinoma reports [16,24]. Another report described a 11-year-old bitch presented with rapid onset of progressing neurologic sings (nystagmus, opisthotonus and seizure) due to a large pituitary corticotroph carcinoma compressing and infiltrating the hypothalamus [2]. In our case report, the dog achieved 30 days of survival time and also presented a rapid progress of clinical deterioration.

In dogs, imaging findings regarding pituitary masses are reported commonly, but there is lack of description for pituitary carcinomas in veterinary literature. Imaging findings in macrotumors include presence of oval or irregular mass measuring more than 10 mm, originating from the pituitary fossa, with homogenous or heterogenous pattern of strong contrast enhancement. In our case report, CT findings reveled a pituitary mass of 2.5 cm in vertical height suggesting a pituitary macrotumor. Therefore, there

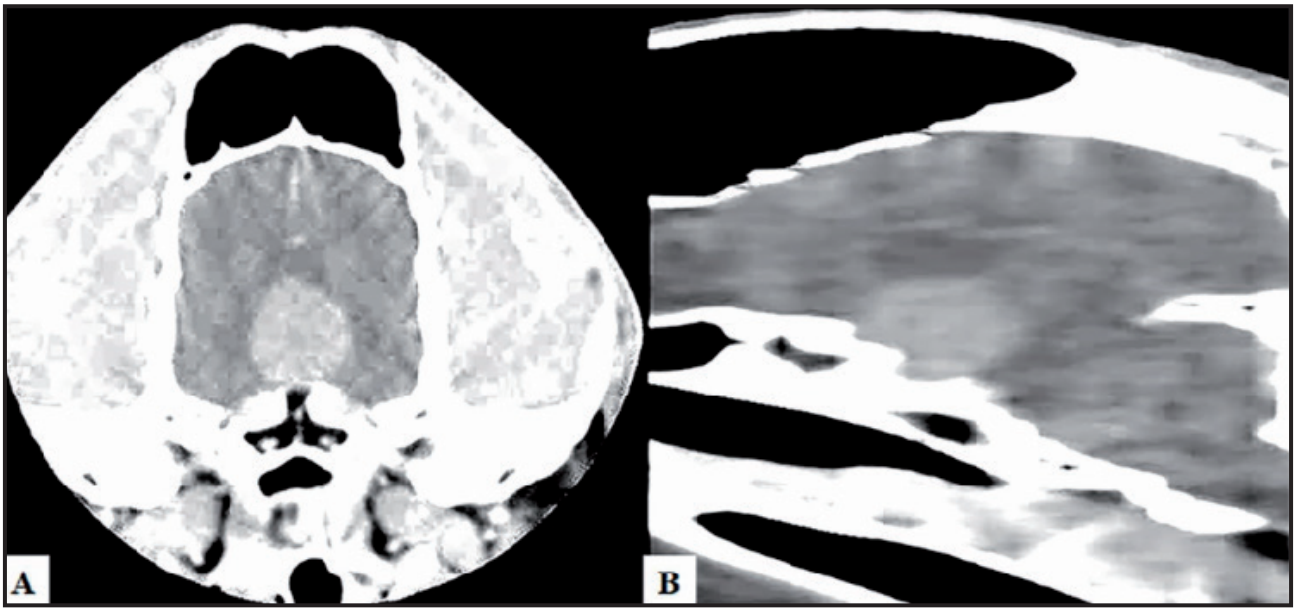

Figure 1. Contrast-enhanced computer tomography (CT) images of a 7-year-old female spayed Golden Retriever. A- Transverse CT image. A well marginated extra-axial mass was evident, with strong contrast enhancement, originating from the sella turcica with supra-sellar expansion and displacement of the third ventricle, measuring about 2.0x1.9x1.9 cm (height, width and length), at the time of diagnosis. B- Sagittal CT image. Moderate mass effect with perilesional edema.

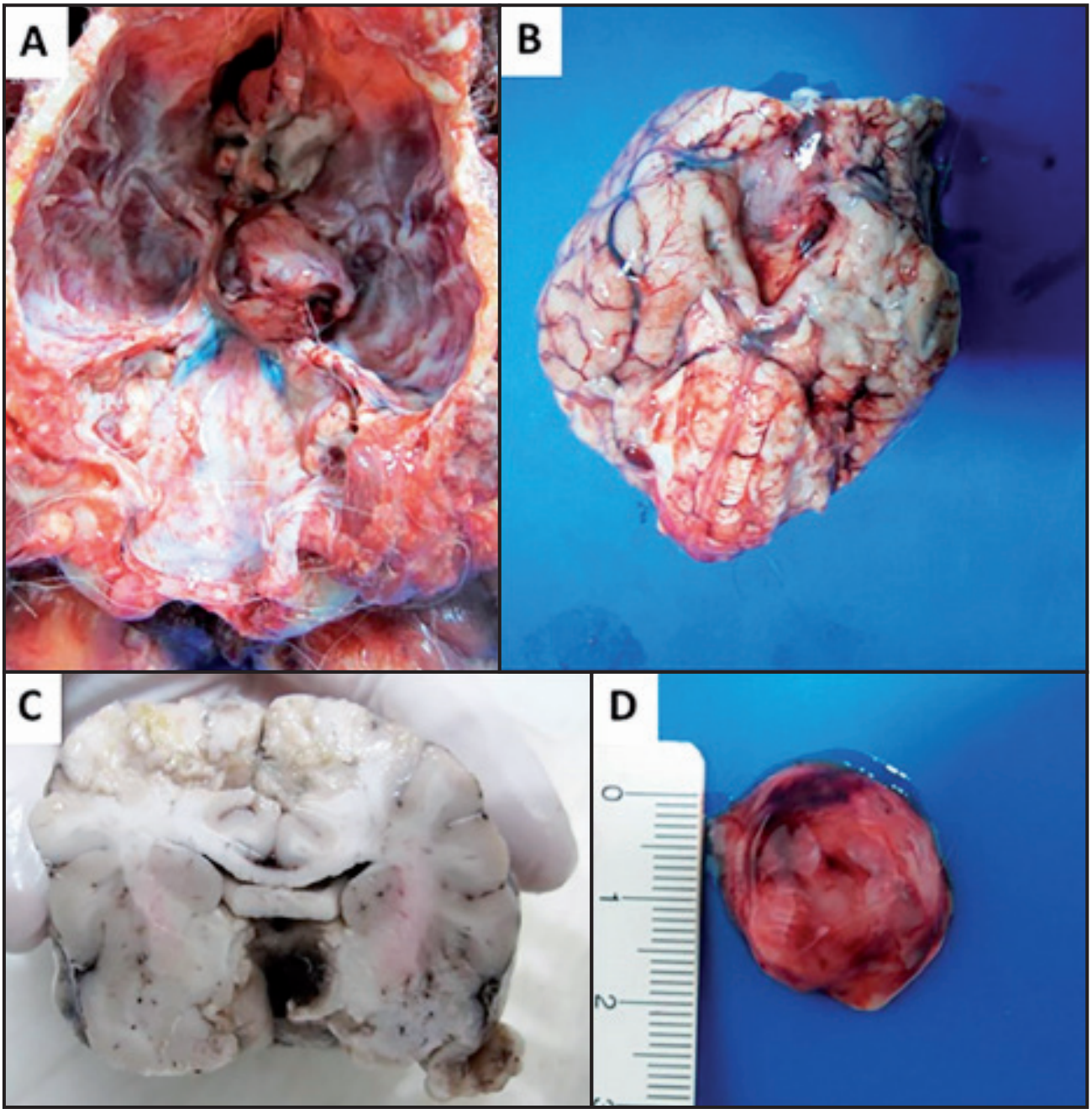

Figure 2. Gross view of Pituitary Carcinoma in a 7-year-old female spayed Golden Retriever. A- Pituitary tumor on the sella turcica promoting the enlargement of the cavity and surface osteolysis of the sphenoid bone. B- Ventral view of the encephalon. Tumor insertion compressed the diencephalons structures (optic chiasma, oculomotor and olfactory nerves, mamillary body, infundibulum, tuber cinereum, III ventriculus and vascular veins). C-Transversal section of the encephalon after 10% formalin buffer fixation. Tumor cavity compressing the diencephalon structures until anterior commissure. D- Pituitary tumor. Round tumor in adenohypophysis, 2,5 x 2,0 cm size.

is a substantial overlap between imaging findings for pituitary adenomas and adenocarcinomas, making impossible to perform this differentiation based only in imaging [10,23].

One of the limitations of this report was the fact that we did not performed the serum endogenous ACTH, however we may suggest that could be normal, since the tumor did not express ACTH receptor. According to database, macroscopic hormone-secreting tumors in dogs may cause distant metastasis [2,8]. In contrast with these case reports, our patient had a hormone-negative secreting tumor and a metastasis in central nervous system was observed.

In our study, the Ki-67 proliferation index was 10% within neoplastic cells. One study evaluated 17 pituitary carcinomas in humans and a median Ki-67 labeling index of 11% (range 1-40%) were observed, with most of the tumors presented a Ki-67 labeling index >3% [19].

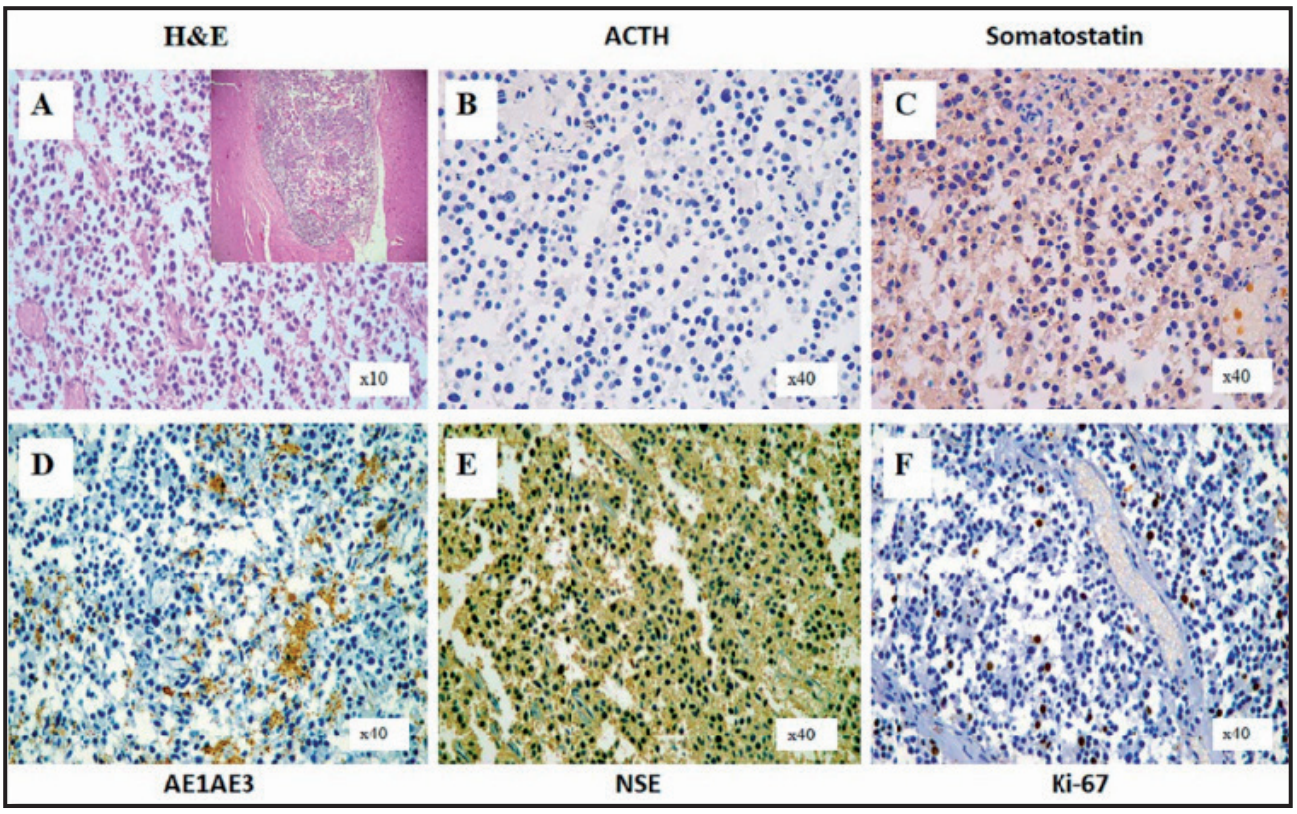

Figure 3. Photomicrographs of Pituitary Carcinoma in a 7-year-old female spayed Golden Retriever. A- Hematoxylin eosin staining (H&E) revealed a non-encapsulated tumor invading into the encephalon, with neoplastic cells arranged in clusters or nests showing pleomorphic round-shaped nuclei, non-granulated, pale eosinophilic cytoplasm and mitotic figures disposed into a fibrovascular stroma. The insert in panel A' shows the histological poorly delimited mass invading the encephalon between the brain hemispheres. B & C- Immunohistochemistry (IHC) showed negative immunoreactivity for ACTH and somatostatin antibodies in the neoplastic cells. D- Positive immunoreactivity for pan-cytokeratin (AE1AE3). E- Strong positivity for Neuron-specific enolase (NSE) antibodies. F- Approximately 10% of the tumor cells presented nuclear expression of Ki67 protein [H&E; 100x & IHC; 400x].

In conclusion, there is a lack of information about pituitary carcinoma in dogs. It is a rare neoplasm with a poor prognosis. A pituitary carcinoma must be considered in patients with a pituitary mass and rapid worsening of the clinical signs, as observed in this case. However, the diagnosis of pituitary carcinoma was only possible due the histopathologic exam and the metastatic focus in central nervous system.

MANUFACTURERS

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Declaration of interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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