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OPHTHALMOLOGICAL AND NEUROLOGICAL MANIFESTATIONS OF A DOG WITH INTRACRANIAL ANAPLASTIC EPENDYMOMA. CASE REPORT

MANIFESTAÇÕES OFTALMOLÓGICAS E NEUROLÓGICAS EM UM CÃO COM EPENDIMOMA ANAPLÁSICO INTRACRANIAL: RELATO DE CASO

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SUMMARY

The objective is to report ependymoma associated with uveitis in a four-month-old male boxer crossbreed. The dog initially presented in both eyes conjunctival hyperemia, blepharospasm, projection of the nictitating membrane, and photophobia, characteristic of uveitis. Traumatic uveitis was rejected. Six days after onset of ophthalmic symptoms, vomiting, incoordination, and behavior changes occurred. Neurological symptoms and eyebrow contraction suggesting head pain and brain injury were investigated by computed tomography (CT) nine days after, when the dog showed spasms of the limbs and neck followed by respiratory arrest with reversal and stabilization. The scans revealed extensive amorphic neoformation in the diencephalon, midbrain, and within the right lateral ventricle, along with sinistral displacement of the cerebral sickle. The animal was euthanized, and necropsy of the head revealed hydrocephalus and an intracerebral tumor mass consistent with the CT imaging. Histopathological evaluation by hematoxylin and eosin staining revealed tissue alterations in several CNS segments, showing several pseudorosettes in the neuropil, mitosis, and a high degree of cell atypia, indicating ependymoma. Inflammatory, hemorrhagic, and necrotic tissue lesions were observed in the brainstem and cerebellum due to compression by tumor tissue and hydrocephalus. The neoplasia was phenotyped by Immunohistochemistry (IHC), and tested positive for the tumoral markers vimentin and glial fibrillary acid protein, confirming intracranial anaplastic ependymoma. Behavior changes and neurological signs resulted from vascular, inflammatory, and degenerative processes in the neuropil caused by neoplasm compression and invasion of brain tissue. Although dogs with ependymoma often present with neurological disease, in the present case, blepharospasm was the first symptom noticed by the owner, and it persisted until euthanasia. According to the literature, and confirmed in the evolution of the current case, the symptoms are related to tumor location and extent and to secondary lesions due to tumor expansion. Clinical symptomatology and complementary laboratory testing, CT, necropsy, histology, and IHC characterized ependymoma, a rare condition in young dogs.

KEY-WORDS: Blepharospasm. Uveitis. Intracranial Neoplasia. Neurological Symptoms.

RESUMO

Objetiva-se relatar um caso de ependimoma anaplásico associado a uveíte em cão macho de quatro meses de idade, mestiço Boxer. O cão apresentou, inicialmente, hiperemia conjuntival, blefaroespasmo, projeção da membrana nictitante e fotofobia bilaterais, sinais característicos de uveíte. Uveíte por causa traumática foi descartada. Seis dias após o início dos sintomas oftálmicos ocorreram vômito, incoordenação motora e alterações de comportamento. Sinais neurológicos e contração das sobrancelhas sugeriram algia na região cefálica. Injúria cerebral foi investigada por tomografia computadorizada (TC) nove dias após o início dos sintomas, quando o cão demonstrou espasmos dos membros e pescoço, seguido por parada respiratória com reversão e estabilização. A TC revelou extensa e amórfica neoformação no diencéfalo, mesencéfalo, e dentro do ventrículo lateral direito, com deslocamento à esquerda da foice cerebral. O animal foi eutanasiado e a necropsia revelou hidrocefalia e uma massa tumoral intracerebral condizente com a imagem da TC. A avaliação histopatológica por coloração hematoxilina e eosina, revelou alterações teciduais em várias áreas do Sistema Nervoso Central (SNC), mostrando várias pseudorosetas no neurópilo, mitose, e um elevado grau de atipia celular, indicando ependimoma. Lesões teciduais inflamatórias, hemorrágicas e necróticas foram observadas no tronco encefálico e cerebelo, devido à compressão do tumor e à hidrocefalia. Amostras da

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neoplasia foram submetidas à análise imuno-histoquímica (IHQ), sendo positiva a expressão dos marcadores tumorais vimentina e proteína glial fibrilar ácida, confirmando ependimoma anaplásico intracranial. As mudanças comportamentais e sinais neurológicos resultaram do processo vascular, inflamatório e degenerativo no neurópilo, causados pela compressão e invasão do tecido cerebral pela neoplasia. Embora cães com ependimoma frequentemente apresentem manifestações neurológicas, no presente caso, blefaroespasmo foi o primeiro sinal clínico observado pelo proprietário, e persistiu até a eutanásia do paciente. Os sinais neurológicos estão relacionados à localização do tumor e extensão das lesões secundárias devidas à sua expansão. Sintomatologia clínica e testes laboratoriais complementares, TC, necropsia, histologia e IHQ caracterizaram ependimoma, que é raro em animais jovens.

PALAVRAS-CHAVE: Blefaroespasmo. Uveíte. Neoplasia Intracranial. Sintomas Neurológicos.

INTRODUCTION

Uveitis is a significant ocular disease in dogs and cats, with anterior uveitis being the most common clinical sign. Its clinical importance is due to associated vision lost and serious systemic inflammatory or infectious disease (HENDRIX, 2008; TOWSEND, 2008; NASCIMENTO, 2016), toxic, traumatic, and non-infectious systemic disease or idiopathy (RENWICK; PETERSEN-JONES, 1998; POWELL, 2002; HENDRIX, 2008; SIMON, 2008). The uvea, through its rich vascularization, can be the site of inflammatory reaction to microorganisms and toxins released in generalized infections and to local infections and subclinical metastases (WALDE et al., 1998).

Ependymoma is a malignant primary tumor of the central nervous system (CNS) of neuro-epithelial origin, that is most often seen in middle-aged to aged animals and reported with higher incidence in brachycephalic dog breeds, and clinical signs vary depending on the location of the tumor within the CNS as well as the degree of compression of adjacent tissue (FENNER, 2004; ZACHARY, 2007; ANDRADE et al., 2015). Microscopically, ependymomas are highly cellular and well vascularized. Cells form perivascular rosettes (pseudorosettes) with nuclear polarity away from the vessel wall, or can be arranged in sheets and bands (KOESTNER; HIGGINS, 2002; ZACHARY, 2007).

The differential diagnosis of ependymomas from other CNS tumors showing pseudorosette patterns is made by the finding of true ependymal rosettes along with uniform consistent glial acidic fibrillary protein (GFAP) and vimentin immunohistochemical staining (SFACTERIA et al., 2010). A presumptive diagnosis of dog CNS neoplasia is usually made by magnetic resonance imaging (MRI) (HORTA et al., 2013; KRAFT et al., 1997; ZHAO et al., 2010) or computed tomography (CT) (HORTA et al., 2013; TURREL et al.,1986). Definitive diagnosis requires analysis of brain tissue samples (HORTA et al., 2013), and spinal cord (UENO et al., 2006).

We report a case of ophthalmological and neurological clinical signs in a dog due to an intracranial ependymoma.

CASE REPORT

This case report was approved by the Ethics Committee on Animal Experiments on May 2008, registration number 53/08.

A four-month-old male boxer crossbreed was brought for ophthalmologic consultation to the veterinary clinic CEMEV, Ubatuba city, SP state, Brazil, having shown signs for three days prior of bilateral ocular discomfort. It presented with normal water and food intake, normal stools and defecation, and normal urine and urination.

General clinical condition: The dog flinched from touch and attempted to escape manipulation. It presented normal heart and respiratory rate and body temperature, normocorated gingival mucosa, hypercorated ocular mucosa, and non-reactive lymph nodes. A hemogram showed thrombocytosis.

Ophthalmological examination: Face was symmetrical and ocular position normal. Photomotor and consensual pupillary response was preserved, but reflex of exacerbated glare, photophobia, and accentuated blepharospasm were evident. Evidence of retropulsion pain, but no resistance or increase in volume of eyeballs. Intense conjunctival and bulbar hyperemia, with reactive lymphoid follicles in bilateral nictitating membranes. Anterior chamber, crystalline and fundoscopy without bilateral changes. Fluorescein negative, bilateral. Deambulation under photopic and scotopic conditions. Oral dipyrone was administered twice daily for four days and 0.1% prednisolone eye drops four times daily for four days.

At reassessment, there was no improvement of the blepharospasm, but the dog showed greater comfort after the administration of dipyrone. Again, the dog attempted escape handling, so a 24 h fast and sedation was applied before a thorough ophthalmological examination. At this second assessment, the owner reported that the dog presented apathy, had experienced bouts of vomiting, and had fallen into a pool. Clinical examination showed normal vital signs. A blood count to assess leukocytosis, neutrophilia, and thrombocytosis and measures of glutamic-pyruvic transaminase, alkaline phosphatase, total protein, and glycemia showed normal values. After a subsequent six day follow-up and treatment, the patient showed evidence of episodes of severe pain. Fentanyl (5mcg/kg IM every 3h) was administered to provide comfort and immediate analgesia. The patient returned to show pain 3 hours after the administration of Fentanyl, which was replaced by Morphine (0.5mg/kg, every 4 hours, IM) due to its longer analgesia. However, because this drug also causes gastric discomfort, it was replaced by Methadone (0.3mg/kg, QID, IM). During the period of treatment with opioid analgesics, an association was made with Dipyrone (25mg/kg BID, SC). The patient presented an intractable pain, which did not completely give in to the medications. The dog began to emit cries and groans, walking around walls, and tachypnea alternated with

eupnea. Contraction of eyebrows suggested head pain, and, in order to investigate a possible cerebral lesion, CT of the skull was done on day nine of investigation. Some hours before the CT examination, the patient suffered severe worsening of symptoms, including limb and neck spasms followed by respiratory arrest. The patient was stabilized and CT was conducted using a tomograph Toshiba® (Alexion 16 channel), helical method - multislice, with 16x1mm collimation, pre- and post-intravenous contrast Omnipaque® (iohexol 300 mgI/mL) at 2 mL/kg. Imaging revealed an extensive amorphous neoformation originating from the right hippocampus and progressing to the right lateral and left ventricle region, exhibiting a marked sinistral displacement of the cerebral sickle and partial loss of definition of the lateral ventricles. The mass occupied a large portion of the diencephalon and midbrain, as well as the interior of the right lateral ventricle. Administration of contrast medium revealed diffuse heterogeneous enhancement of approximately 3.8 x 3.5 x 4.3 cm (Figure 1).

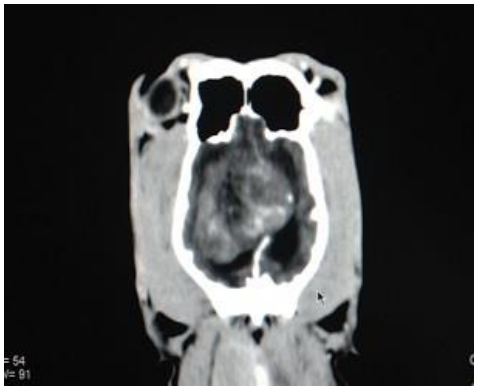

FIGURE 1 - Computed tomography. Amorphous neoformation originating in the right hippocampus and progressing to the right lateral ventricle and to the left side, producing displacement of the cerebral sickle to the left and partial loss of definition of the lateral ventricles (yellow arrow). Helical-multislice method. Collimation 16 x 1 mm

Due to the severity of the clinical condition and grave prognosis, the animal was euthanized following the CFMV (2012) protocol.

A complete necropsy was performed, in order to assess the involvement of CNS and other organs (lung, heart, spleen, liver, adrenals, kidneys, lymph nodes). As the CT indicated a tumor mass, the head of the animal was necropsied to obtain CNS tissue samples for definitive histophalogical diagnosis (HORTA et al., 2013). Removal of the skull cap revealed hydrocephaly. The cerebral hemispheres, cerebellum, brainstem, and cervical spinal cord were removed for macroscopic analysis. A 5.5 x 3.0 x 2.5 cm gray, well-demarcated, soft-textured mass was found, mostly located in the right ventricle, which dislocated the scythe of the brain and invaded the left ventricle and extended into the thalamus; the cortical regions of the right and left cerebral hemispheres were thinner, and the right lateral ventricle was much dilated due to hydrocephalus (Figure 2).

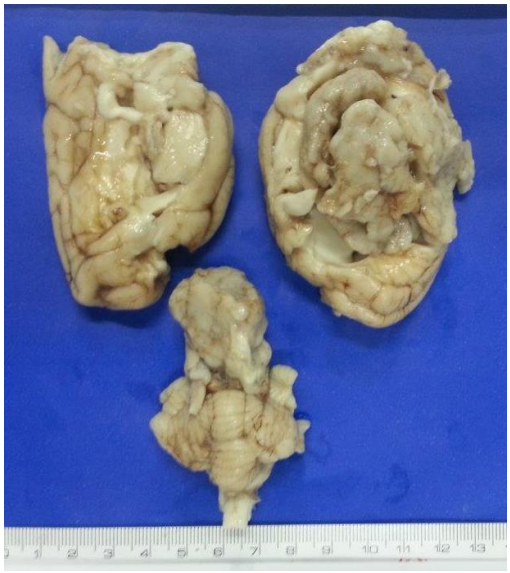

FIGURE 2 - The neoplasia in the right ventricle (yellow arrow) dislocated the scythe of the brain, invaded the left ventricle (green arrow), and extended to the thalamus (red arrow). The cortical regions of the right and left cerebral (blue arrow) hemispheres were less thickened.

Fragments of CNS and tumor tissue were fixed in 10% buffered formalin, and were cut into small pieces, dehydrated, cleared, and embedded in paraffin (PROPHET, 1995). Three µm sections were cut and stained with hematoxylin and eosin. Histopathological evaluation by light microscopy did not reveal changes in lung, heart, spleen, liver, adrenals, kidneys, and lymph nodes. The CNS revealed tissue alterations in several segments (Table 1), showing several pseudorosettes in the neuropil, mitosis figures, and a high degree of cell atypia (KOESTNER; HIGGINS, 2002; MAXIE; YOUSSEF, 2007; ZACHARY, 2007). Inflammatory, hemorrhagic, and necrotic tissue lesions were observed in the brainstem and cerebellum due to compression by tumor tissue and hydrocephalus.

Table 1- CNS anatomical segments and microscopic description of observed lesions.

CNS Anatomical segment	**Microscopic observations**
Cervical spinal cord	Dilatation of the ependymal canal, neuropil vessels and meningeal congestion
Obex and cerebellar Peduncle	Multiple hemorrhagic foci on the neuropil of the 4th ventricle floor.
Cerebellum	Multiple hemorrhagic foci in the cerebellar convolutions. Purkinje cell degeneration and necrosis. Meningeal congestion.
Caudal and rostral colliculus	Discrete perivascular hemorrhagic foci. Meningeal and neuropil congestion.
Thalamus	Dark and retracted neurons, edema and neuropil congestion. Meningeal congestion. Tumoral tissue arranged in pseudorosettes, neovascularization, mitotic figures, evident nucleoli, laterally located nucleus, and high degree of cellular pleomorphism (anisocytosis and anisocariosis).
Right frontal, parietal and occipital cortex	Dark and retracted neurons, cortical spongiosis, neuropil and meningeal congestion, discrete mononuclear inflammatory infiltrate, meningeal hemorrhage.
Right tumor adhered in cortex temporal	Tumor formations arranged in pseudorosettes with neovascularization at the edge of the neuropil (cortical region), mitotic figures, evident nucleoli, laterally located nucleus, high degree of cellular pleomorphism (anisocytosis and anisocariasis)
Right diencephalon	Meningeal and neuropil congestion, cortical spongiosis, discrete mononuclear inflammatory infiltrate.
Left frontal, temporal, parietal and occipital cortex	Meningeal and neuropil congestion, dark and retracted neurons, cortical spongiosis and discrete mononuclear inflammatory infiltrate.
Left diencephalon	Meningeal and neuropil congestion, hemorrhagic foci with dark and retracted neurons, cortical spongiosis and discrete mononuclear inflammatory infiltrate.
Tumoral mass inside both ventricles	Tumor formations arranged in pseudorosettes with small central lumen and in leaflets or cell groups without a discernable distribution pattern. Tumor cells with high degree of cellular pleomorphism (anisocytosis and anisocariasis), circular or oval nucleus and moderately hyperchromatic eosinophilic cytoplasm with poorly defined borders, neovascularization, mitotic figures, evident nucleoli.

Tumor phenotyping was performed by immunohistochemistry (IHC) (VAN DER WOERDT, 2001; VURAL et al., 2006; UENO et al., 2006).

Antigen retrieval employed citrate buffer at pH 6.0 with 18 hours incubation at 4°C. The non-biotinylated polymer amplification ENVISION/HRP (Dako®, Carpinteria, CA, USA) was used as the detection system (Avidin-Biotin Immunohistochemistry) (KEY, 2006) according to the manufacturer's protocol. The panel of primary antibodies used for tumor immunophenotyping (Table 2) were vimentin (intermediate filament of mesenchymal cells) clone V9 at 1:200 dilution, polyclonal glial fibrillar acid protein (GFAP 9) at 1:300 dilution, PAN-CK (intermediate filaments of epithelial cells) clone AE1AE3 at 1:200 dilution, E cadherin (cell adhesion molecule) clone NHC-38 at 1:50 dilution, synaptophysin (neuroendocrine cell marker) clone SY38 at 1:100 dilution, neuron-specific enolase (NSE) clone BBS/NC/HIV14 at

1:1000 dilution, and polyclonal S100 (neuroglial, ependymal, melanocytic and Schwann cells marker) at 1:1000 dilution. For visualization of development of the reaction, the chromogen diaminobenzidine (DAB) (Dako®, Carpinteria, CA, USA) was used according to the manufacturer's protocol. The sections were counterstained with hematoxylin and eosin and examined under optical microscope to verify the positive brown staining in the cytoplasm and nuclei.

Table 2 - Panel of primary antibodies used for tumor immunophenotyping.

Antibodies	Clone	Dilution	Immunostaining in neoplastic cells
Vimentin	V9	1:200	Positive
GFAP 9	Polyclonal	1:300	Discrete and sparse positivity
PAN-CK	AE1AE3	1:200	Negative
E cadherin	NHC-38	1:50	Negative
Synaptophisyn	SY38	1:100	Negative
NSE	BBS/NC/VIH14	1:1000	Negative
S100	Polyclonal	1:1000	Negative

The immunolabeling of the neoplasia was positive by IHC for vimentin (Figure 3B) and GFAP 9 (Figures 3C and 3D) and negative for PAN-CK (Figure 3E), E cadherin (Figure 3F), synaptophysin (Figure 3G), and S100 (Figure 3H). The features of the neoplasm were most consistent with anaplastic ependymoma (Table 2) (KOESTNER; HIGGINS, 2002; SFACTERIA et al., 2010).

DISCUSSION

Uveitis is often the first manifestation of systemic disease (POWELL, 2002). The initial symptoms presented in the current case were conjunctival hyperemia, blepharospasm, projection of the nictitating membrane, and photophobia, characteristic of uveitis (RENWICK; PETERSEN-JONES, 1998).

Bilateral ophthalmic inflammatory involvement observed in the reported case could have been related to anterior uveitis resulting from the hyperviscosity syndrome present in neoplastic and paraneoplastic alterations, or even in response to chemical mediators of inflammation (ORIÁ et al., 2004; GELLAT, 2003). The uveitis may be associated with inflammation resulting from the growth of the neoplasm in the CNS. The ependymoma caused compression, hemorrhagia and inflammation of the cortical neurophil by tumor expansion and hydrocephalus from the frontal, temporal, parietal, and occipital cortex to the diencephalon.

The condition described here in a four-month-old dog is rare and runs counter to the scientific literature, which reports ependymoma to commonly occur in middle-aged to aged animals (MAXIE; YOUSSEF, 2007; TRASLAVINA et al., 2013). A higher incidence is reported in the brachycephalic dog breeds (KOESTNER; HIGGINS, 2002; MARCH, 2003, VURAL et al., 2006, ZACHARY, 2007). This young dog was a boxer crossbreed.

Although dogs with ependymoma often present with neurological disease (ZACHARY, 2007), in the present case, blepharospasm was the first symptom noticed by the owner, and it persisted until euthanasia. According to the literature, and confirmed in the evolution of the current case, the symptoms are related to tumor location and extent and to secondary lesions due to tumor expansion (FENNER, 2004; ZACHARY, 2007; ANDRADE NETO et al., 2015). Computed tomography was used to investigate the structure of the dog's brain (TURREL et al., 1986), and findings were confirmed by necropsy: the tumor extended from the thalamus to both lateral intraventricular spaces, compressing the right and left cerebral cortex and diencephalon, and causing hydrocephalus (Figura 1, 2 and 3), as described in other cases (KOESTNER; HIGGINS, 2002; MAXIE; YOUSSEF, 2007; ZACHARY, 2007; GUAN et al., 2011; HORTA et al., 2013). The microscopic lesions in the CNS (Table 1) confirmed compression of the cortical neurophil by tumor expansion and hydrocephalus from the frontal, temporal, parietal, and occipital cortex to the diencephalon (FENNER, 2004; ZACHARY, 2007; ANDRADE NETO et al., 2015).

The tumor invasion of the thalamus caused hemorrhagia and necrosis of the neurophil. The cerebellum and brainstem were compressed by hydrocephalus, causing hemorrhage and necrosis of the neurophil (Table 1) (FENNER, 2004; ZACHARY, 2007; ANDRADE NETO et al., 2015).

The gross and microscopic lesions can explain the clinical evolution of the case: The blepharospasm resulted from lesions in the basal ganglia and upper midbrain, and bulbar and cerebellar injury produced incoordination, vomiting, and respiratory arrest (EMOTO et al., 2011).

Sudden-onset clinical signs have been previously reported in an intracranial malignant ependymoma in a boxer breed dog (BORRELLI et al., 2009).

Based on the presence of prominent perivascular pseudorosettes, ependymoma, papillary meningioma, and paraganglioma were considered in the IHC differential diagnoses. Immunohistochemical staining was conducted (KEY, 2006), showing the features of the neoplasm to be consistent with anaplastic ependymoma (Table 2). Multiple subtypes of ependymomas have been described (VURAL et al., 2006), including some that lack the characteristic papillary pattern and rosette formation expected in classic tumors. The relatively few studies that have examined biomarkers in animal ependymomas have reported positive vimentin staining and GFAP reaction, although an ependymoma in the cervical spinal cord not expressing GFAP and slightly positive for vimentin and cytokeratin was identified in an 8.5-year-old Maltese dog (MICHIMAE et al., 2004).

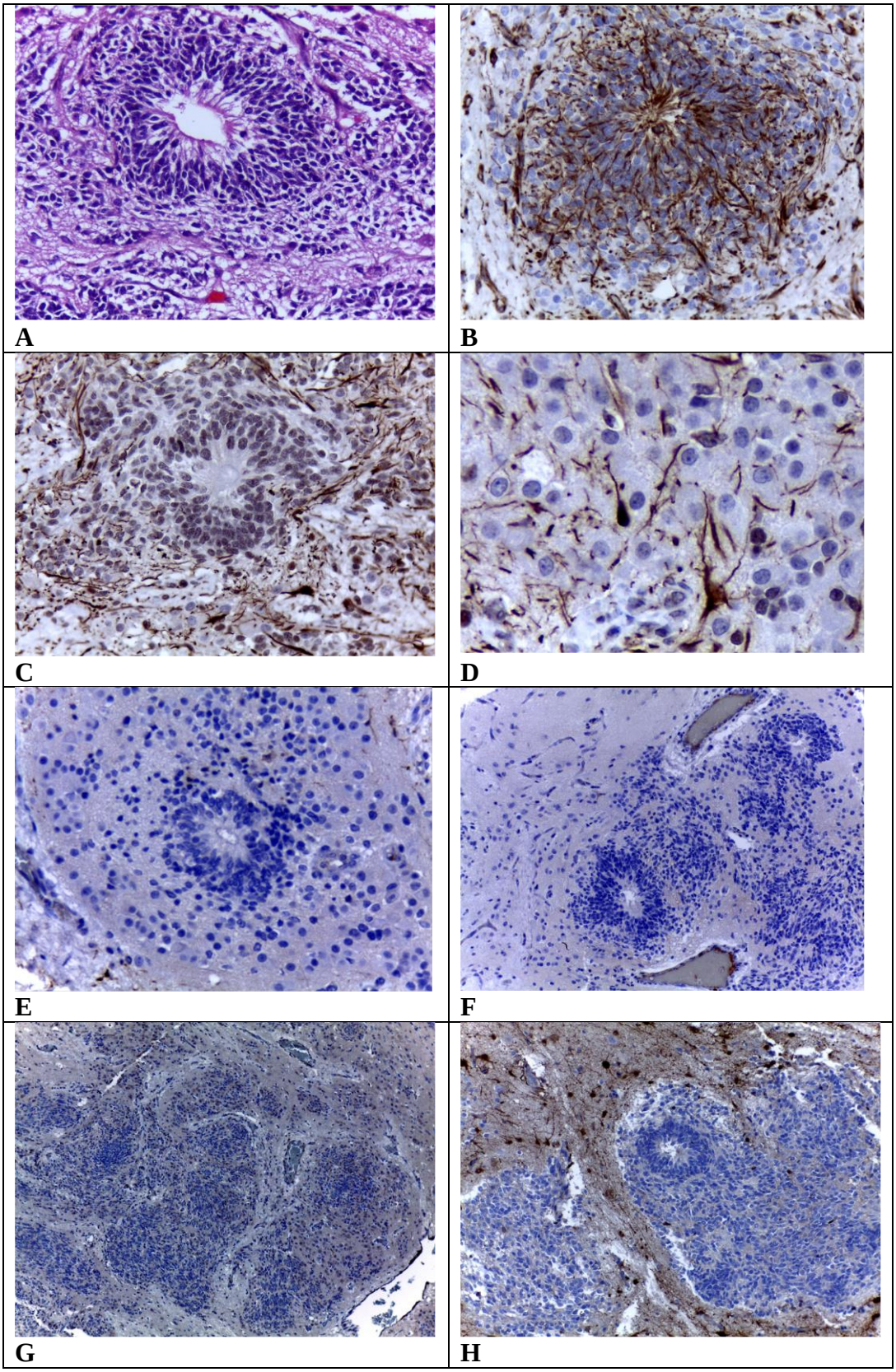

FIGURE 3 - Histopathology, CNS, ependymoma, dog. A-) H&E staining, 400x. B-) Positive immunostaining for Vimentin, 400x. C-) and D-) discrete positive immunostaining for GFAP 9, 400x and 600x, respectively. E-) Negative immunostaining for PAN-CK, 400x. F-) Negative immnunostaining for E cadherin, 200x. G-) Negative immunostaining for synaptophysin, 100x. H-) Negative immunostaining for S100, 100x.

A case of similar oculocephalic and behavior responses and generalized ataxia in a nine-year-old German Shepherd associated with ventricular ependymoma has been reported (VURAL et al., 2006). This case report was complemented by MRI, macroscopic evaluation, and immunohistology. The 5.5 x 3.0 x 2.5 cm ependymoma, localized intra-axially in the right interventricular foramen and hydrocephalus was detected by MRI.

Microscopically, the tumor was composed of pseudorosettes, and immunohistochemical examination revealed vimentin and GFAP immunoreactivity in the neoplastic cells. According to the literature, these primary antibodies were identified in ependymomas (KOESTNER; HIGGINS, 2002; SFACTERIA et al., 2010).

It is essential to differentiate primary brain tumors from secondary metastatic tumors (MOORE et al., 1996). Studies of causes of intracranial tumors in the CNS of dogs are imperative to aid in differential diagnosis, to provide a prognosis, and recommend treatment or euthanasia. Ultrasonography, computed tomography, magnetic resonance, and nuclear medicine are noninvasive and offer high-resolution cross-section images that help the clinician correlate symptoms with disease (TUCKER; GAVIN, 1996).

In the current case, the CT was fundamental in demonstrating that the ophthalmic symptoms resulted from the irreversible expansion of intracerebral lesion, allowing an unfavorable prognosis and the final decision of euthanasia. Neoplasms of the CNS in dogs typically cause progressive neurological signs in aged animals, with ataxia and behavior changes common (VURAL et al., 2006), many produce localized signs detected on neurological examination and allow an anatomical diagnosis (HORTA et al., 2013). Secondary changes such as obstructive hydrocephalus, cerebral edema, herniations, and tumor expansion may produce more wide-spread deficits (HORTA et al., 2013).

Research is critical to understanding the molecular aspects of ependymoma, and to the development of a targeted therapeutic strategy (GUAN et al., 2011). Because it is a rare neoplasm in dogs, studies of the biology of ependymoma and other CNS neoplasia should be expanded, detailing the clinical history and evolution of the disease.

CONCLUSION

The comprehensive clinical investigation of an ophthalmologic case, followed through significant neurological disease evolution, culminated in diagnosis of clinical pathology via computed tomography, necropsy, CNS histology, and tumor phenotyping by immunochemistry, elucidated a rare case of ependymoma in a young dog.

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