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Case Report

Horner's Syndrome Associated with Glioblastoma Multiforme in a Dog

Aline de M. Viott [1], Roselene Ecco[1], Carla M.O. Silva[2], Gustavo O. Fulgêncio[2], Eliana G. Melo[1], Ingeborg M. Langohr[3]

[1] Departamento de Clínica e Cirurgia Veterinárias, Escola de Veterinária, Universidade Federal de Minas Gerais - UFMG, Brazil.
[2] Veterinary School, Universidade Presidente Antônio Carlos – UNIPAC. Conselheiro Lafaiete. Minas Gerais, Brazil.
[3] Veterinary School, Michigan State University, Lansing, MI. USA.
[*]**Corresponding author**: Roselene Ecco, Departamento de Clínica e Cirurgia Veterinárias, Escola de Veterinária, UFMG, Belo Horizonte, MG, CEP 30123-970 Brasil. E-mail: ecco@vet.ufmg.br

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Abstract

A 7-year-old, intact female Bulldog was presented to the veterinarian with ocular signs characteristic of Horner's Syndrome: bilateral conjunctival hyperemia, enophthalmos, miosis, and protrusion of the third eyelid of left eye. A month later, the dog returned for recheck with marked neurologic signs: lethargy, circling, constant vocalizing, depressed mentation, and hyperesthesia. A neoplasm in the brain was suspected. Treatment was implemented in an attempt to reduce clinical signs. After initial clinical remission, the clinical condition got worse and the owner elected euthanasia. Necropsy revealed a large intracranial neoplasm affecting an extensive portion of the cerebral parenchyma. The neoplasm was histologically diagnosed as glioblastoma multiforme. Determination of the extent of the affected cerebral regions based on neurologic exam was useful in establishing the presumptive clinical diagnosis of intracranial neoplasm. Horner's syndrome preceded the neurologic signs in this dog. Although intracranial neoplasms such as glioblastomas multiformes are a rare cause of this syndrome, it is important to include them in the list of differential diagnoses in dogs in which this syndrome is seen in conjunction with neurologic signs.

Key words: canine, Horner's syndrome, intracranial neoplasia, pathology, glioblastoma multiforme

Description

In veterinary medicine, astrocytomas are considered rare neoplasms that affect primarily old and brachycephalic dogs (13). Glioblastoma multiforme (GBM) is defined as grade IV astrocytoma (7, 13) Because of its invasiveness, this neoplasm is regarded as highly malignant, resulting in severe clinical signs that frequently culminate in the death of the animal (5, 7).

Horner's syndrome is caused by loss of sympathetic innervation of the globe and its adnexal structures (1). In dogs, this clinical syndrome is characterized by miosis, ptosis, prolapse of the nictitating membrane, conjunctival vasodilation, and apparent enophthalmos (3, 16). Reported causes include otitis media and interna, brachial plexus root avulsion, cervical intervertebral disk protrusion, catheterization of the common carotid artery, infections of the central nervous system (CNS), and intracranial neoplasms (3, 6). This article describes the clinical and pathologic findings in a dog with Horner's syndrome associated with GBM. Clinical signs, including ocular disturbances, are discussed in detail in correlation with the localization of the neoplasm.

A 7-year-old, intact female Bulldog was presented to a veterinary neurologist with a history of constant howling, circling, stumbling over objects, and staring for a long time at a fixed point. One month prior to presentation, the dog had been submitted to an ocular exam that had revealed bilateral conjunctival hyperemia, enophthalmos, miosis, and protrusion of the third eyelid of left eye (Fig. 1), a group of signs that is characteristic of Horner's syndrome. The dog had also been diagnosed with hip dysplasia, for which it was being treated with acupuncture.

At the beginning of the neurologic exam, the dog was in stupor. It took approximately 10 minutes to react to constant stimulation by the owner. The dog continued indifferent to its surroundings, but was hyperexcitable to touch. When stimulated, it presented compulsive circling, directed to both the left and the

right side. It presented menace response, but often stumbled over objects. Pain sensation and proprioception were normal in all limbs.

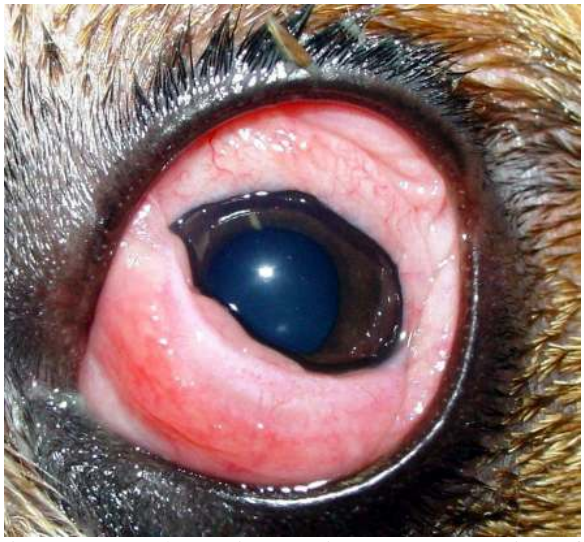

Figure 1 - Ocular region, canine. Note protrusion of the third eyelid, conjunctival hyperemia, enophthalmos, and mild mydriasis 30 minutes after application of 10% phenylephrine (cloridrato de fenilefrina a 10%, ALLERGAN).

An intracranial neoplasm was suspected. Initial treatment attempted to ameliorate consciousness and prevent cerebral edema and hemorrhage. Piracetam[1] (25 mg/kg, PO, q 12 h) was administered for three weeks. The clinical picture worsened and prednisone[2] (2 mg/kg, PO, q 12 h) was added to the treatment protocol for five days. Initially, the dog had apparent clinical improvement. It alternated periods during which it was calm and ate spontaneously with periods during which it presented with agitation, howling and circling, and periods of deep sleep from which it was difficult to recover. After a few weeks, clinical signs got progressively worse, with exacerbation when reducing the dose of the corticosteroid. The dog was maintained on prednisone (0.5 mg/kg, PO, q 12 h) for three additional weeks. The dog also received ranitidine[3] (2mg/kg, PO, q 12 h) to prevent stomach ulcers. Four months later, the dog was totally unresponsive to the environment and owner, and did not voluntarily ingest food and water anymore. Episodes of stupor alternated with episodes of compulsive circling. Due to poor prognosis, the owner elected euthanasia.

At necropsy, there was moderate hydrocephalus, affecting primarily the lateral ventricles, associated with a grayish white, soft, granular, gelatinous mass with multifocal lightly red areas of hemorrhage. The mass was located mostly in the subcortical basal nuclei and peduncles of the piriform lobe and projected dorsally through the trunk of the corpus callosum, abutting the ependyma and compressing the subcortical white matter. It displaced the internal capsule, extended up to the rostrum of the corpus callosum, and compressed the diencephalon (hippocampus and thalamus). Distally, the mass extended to the cranial colliculi in the mesencephalon, resulting in dilation of the mesencephalic aqueduct. Laterally, the mass extended into the cerebral hemispheres, partially filling the lumen of the lateral ventricles (Fig. 2).

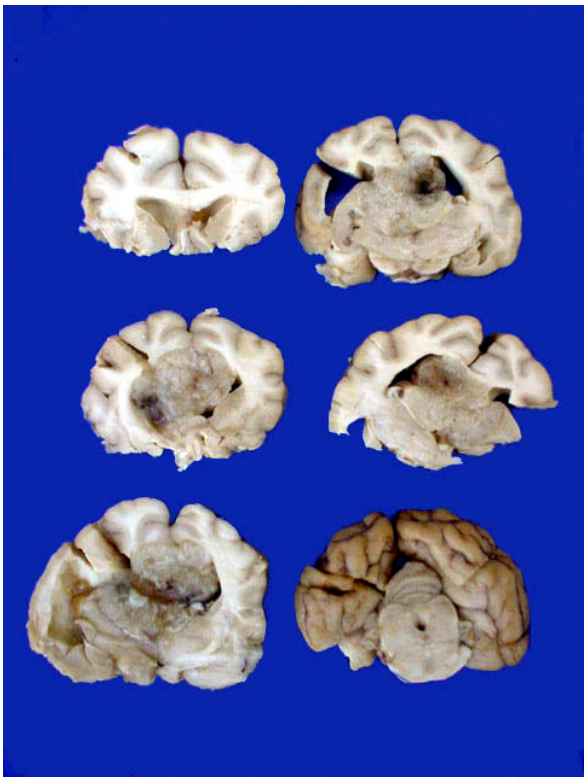

Figure 2 - Brain, canine, glioblastoma multiforme. Transverse sections of the brain reveal an infiltrative, grayish-white, soft neoplastic mass. The neoplasm is located mostly within the telencephalon (subcortical basal nuclei and peduncles of the piriform lobes) and projects dorsally through the trunk of the corpus callosum, abutting the ependyma and compressing the subcortical white matter. It displaces the internal capsule, extends up to the rostrum of the corpus callosum, and compresses the diencephalon (hippocampus and thalamus). Distally, the mass extends to the cranial colliculi of the mesencephalon, causing dilation of the mesencephalic aqueduct. Laterally, the mass extends into the cerebral hemispheres, partially filling the lumen of the lateral ventricles.

The whole brain and samples of multiple organs were fixed in 10% buffered formalin and were routinely processed for histopathology. Histologically, the mass consisted of lacy sheets of neoplastic cells with indistinct margins, ample eosinophilic, moderately vacuolated cytoplasm, and large, round to oval nuclei with prominent nucleoli and variable chromatin

[1] Exit®- FARMASA. Laboratório Americano de Farmacoterapia S/A. São Paulo. São Paulo. Brazil.
[2] Meticorten® - Shering-Plough S.A. São Paulo. São Paulo. Brazil.
[3] Label® - Asta Médica Ltda. São Paulo. São Paulo. Brazil.

pattern. There was marked anisocytosis and anisokaryosis; mitotic figures were common (> 6 per high power field). Multifocal to coalescing extensive areas of necrosis were present, accompanied by hemorrhage and surrounded by pseudopalisading neoplastic cells (Fig. 3). Intralesional microvascular proliferation was prominent. Interspersed among the neoplastic cells were occasional deposits of amorphous eosinophilic material consistent with osteoid. Histologic findings were characteristic of GBM (7). To further confirm the astrocytic origin of the neoplastic cells, immunohistochemistry for vimentin, cytokeratin, and glial fibrillary acid protein (GFAP) was performed (11). Neoplastic cells were positive for vimentin and were negative for cytokeratin and GFAP.

GBMs are rare neoplasms that composed 2.9% of the neoplasms in the CNS of dogs in a large study of primary intracranial neoplasms (12). These tumors can cause compression of the surrounding brain parenchyma due to its space-occupying effect (7). The dog in this case had clinical signs classic for CNS lesions affecting the cranial portion of the brain (telencephalon and diencephalon) and the midbrain (mesencephalon), such as circling, changes in behavior, stupor, depression, and unresponsiveness to the environment. Such variable clinical manifestations are common in extensive brain diseases (9). The severity of associated clinical signs increases as the neoplasm grows, and the clinical manifestation gets more variable as the neoplasm involves more extensive areas of the cerebral parenchyma. Behavioral abnormalities are commonly observed in association with neoplasms in the brain (7).

Lesions that affect the frontal lobe of the cerebrum frequently cause disinhibition that may be characterized by compulsive and random walk. If the lesion is unilateral or asymmetric, the animal tends to walk in circles, generally to the same side as the lesion (2, 10). In this case, the dog circled to both sides, reflecting the extensive invasion of the cerebral hemispheres by the neoplasm. Lesions affecting the cerebral hemispheres and the basal nuclei may also lead to behavioral disturbances and blindness (4). The dog also had apparent blindness with maintenance of the pupilar reflex. This is consistent with central blindness, which is associated with lesions in the occipital cortex and/or midbrain (9). These brain structures were compressed and invaded by the neoplasm.

Lesions located in the brainstem cause mainly alterations of the cranial nerves, as well as depression and paresis. Stupor, disorientation and unresponsiveness to the environment are additional clinical signs associated with proliferative lesions that are located in the cerebral cortex and compress the brainstem. These signs are associated with the disruption of impulse conduction between cerebrocortical neurons and neurons in the ascending reticular activating system. Alterations in the equilibrium between these two networks of neurons can produce clinical signs that vary from hyperexcitability to coma (10).

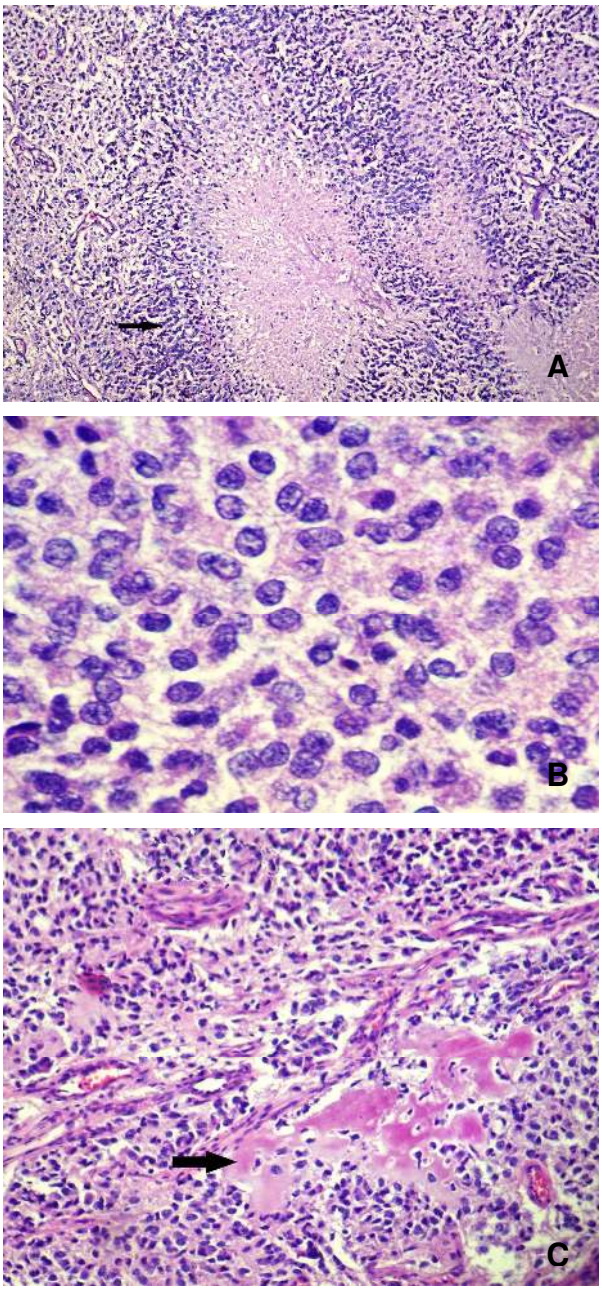

Figure 3 - Brain, canine, glioblastoma multiforme. A. Extensive areas of necrosis are surrounded by pseudopalisading neoplastic cells (arrow). Hematoxylin & Eosin (H&E). Obj. 10x. B. Neoplastic cells have large, oval nuclei, ample eosinophilic cytoplasm, and indistinct cell borders. There is marked anisokaryosis and anaplasia. H&E. Obj. 40x. C. Deposits of amorphous eosinophilic material consistent with osteoid (arrow) are interspersed among the neoplastic cells. H&E. Obj.20x.

The ocular signs, characteristic of Horner's syndrome, were the first ones to be recognized in this case. Horner's syndrome is the name given to a group of signs that result from the interference of the sympathetic innervation of the globe and its adnexal structures. The sympathetic innervation of the globe

can be anatomically divided into a three neuron chain composed of central, pre-ganglionic and post-glanglionic neurons (3). The central sympathetic fibers originate in the hypothalamus (forebrain), tectum and tegmentum (midbrain), pass through the lateral pons, medulla oblongata and cervical spinal cord, and synapse with pre-ganglionic neurons in the first thoracic spinal cord segments. Fibers of the latter neurons join the vagosympathetic trunk and synapse with the post-ganglionic neurons in the cranial cervical ganglion. Some of their fibers course with the fibers of the ophthalmic nerve that radiate out into the ocular orbit, glands, and regional muscles (3, 15).

The ocular signs noted in this dog may have been associated either with loss of central neurons in the hypothalamus, or with discontinuity along the path of the nerve fibers in the midbrain, which were both areas affected by the neoplasm. The sympathetic nerves to the eye innervate the dilator muscles of the iris and smooth muscle of the periorbita, eyelids and third eyelid. The signs of Horner's syndrome (ptosis, enophthalmos, third eyelid elevation and vasodilation) typically accompany miosis when there is damage to the pathways (14).

Histologically, GBMs in canine are frequently composed of fusiform cells with marked anaplasia, anisokaryosis and high mitotic activity. These findings are those of astrocytomas in general; extensive necrosis and microvascular proliferation are required for the diagnosis of GBM (3, 8).

The type of cell that originates GBMs has long been a topic for discussion and research. Traditionally, it was thought that these tumors developed from astrocytes, thus their classification as grade IV astrocytomas. This assumption was based on certain morphologic and immunohistochemical similarities between the astroglial cells and the neoplastic cells of GBMs. Additionally, astrocytes are among the few cell lineages that have the ability to proliferate in the mature brain. However, a recent study showed the presence of pluripotential neural progenitor cells in astrocytomas and GBMs, which explains the mixed glial differentiation noted in these tumors (13). The neoplasm in this case had multifocal osteoid deposits. The mesenchymal component of the gliomas may present a variety of patterns, further corroborating the pluripotential origin of the neoplastic cells (8).

A reliable marker for astroglial cells is GFAP; however, GFAP positivity is quite variable among neoplastic cells in GBMs. Well differentiated cells with ample cytoplasm resembling astrocytes have intense labeling. In contrast, poorly differentiated cells have weak or no labeling (13), similar to that seen in this case. Antibodies against vimentin can be used as additional cell marker of astrocytomas because these neoplasms are generally positive for this marker (7).

This case illustrates the importance of determining the location and extension of a lesion in the CNS of patients with neurologic signs. The differential diagnosis is then based on this anatomic diagnosis and the evaluation of the signalmente and history. Intracranial neoplasms, such as GBMs, can induce a wide variety of neurologic syndromes as well as ocular alterations consistent with Horner's syndrome as observed in this dog. GBMs should therefore be considered in the differential diagnoses of cases with such clinical manifestation.

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