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CASE REPORT

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# Astrocytoma in a french bulldog: 218 days of survival with conservative treatment

Astrocitoma em um buldogue francês: 218 dias de sobrevida com tratamento conservador

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**ABSTRACT:** Glioma is the second most common primary intracranial tumor in dogs and is highly prevalent in brachycephalic breeds. This work aims to report a case of astrocytoma, which is a glioma subtype, in a canine with a survival of 218 days with conservative treatment. In this report, a 7-year-old French bulldog was seen with a history of cluster seizures. To control seizures, phenobarbital 50 mg (3.8 mg/kg, PO, BID) was prescribed. Magnetic resonance imaging (MRI) examinations and collection and analysis of cerebrospinal fluid (CSF) were requested. The MRI report showed intra-axial formation, whose main differential diagnosis included a neoplastic process such as glioma. The patient remained clinically well for 218 days, using only phenobarbital. Two hundred and sixteen days after diagnosis, the patient suddenly presented a reduction in consciousness, which progressed to stupor and death within 48 hours. A necropsy and histopathological examination were carried out, which resulted in the neoformation being classified as astrocytoma. Despite the variety of treatments described to treat gliomas, no gold standard treatment protocol has been recognized to optimize the survival of animals in this category of conditions. The patient in this report had a longer survival rate than the average described in the literature. He remained well for 155 days with phenobarbital and another 63 days with the combination of prednisolone. It is concluded, therefore, that the approach and treatment of gliomas are challenging, and that the definition of which treatment provides a better quality of life and longer survival is still uncertain.

**Keywords:** dog disease; neuropathy; neoplasm; glial cells; astrocyte.

**RESUMO:** O glioma é o segundo tumor intracraniano primário mais comum em cães e é altamente prevalente em raças braquicefálicas. Este trabalho tem como objetivo relatar um caso de astrocitoma, um subtipo de glioma, em um cão com sobrevida de 218 dias sob tratamento conservador. Neste relato, um buldogue francês de 7 anos de idade foi atendido com histórico de crises convulsivas em salva. Para o controle das crises, foi prescrito fenobarbital 50 mg (3,8 mg/kg, via oral, duas vezes ao dia). Foram solicitados exames de ressonância magnética (RM) e coleta e análise do líquido cefalorraquidiano (LCR). O laudo da RM mostrou formação intra-axial, cujo principal diagnóstico diferencial incluía um processo neoplásico como o glioma. O paciente permaneceu clinicamente estável por 218 dias, utilizando apenas fenobarbital. Duzentos e dezesseis dias após o diagnóstico, o paciente apresentou subitamente redução do nível de consciência, que progrediu para estupor e óbito em 48 horas. Foram realizadas necropsia e exame histopatológico, que resultaram na classificação da neoformação como astrocitoma. Apesar da variedade de tratamentos descritos para gliomas, nenhum protocolo de tratamento padrão-ouro foi reconhecido para otimizar a sobrevida de animais nessa categoria de condições. O paciente deste relato apresentou uma taxa de sobrevida maior do que a média descrita na literatura. Ele permaneceu bem por 155 dias com fenobarbital e por mais 63 dias com a combinação de prednisolona. Conclui-se, portanto, que a abordagem e o tratamento de gliomas são desafiadores e que a definição de qual tratamento proporciona melhor qualidade de vida e maior sobrevida ainda é incerta.

**Palavras-chave:** doença canina; neuropatia; neoplasia; células da glia; astrócito.

## INTRODUCTION

Intracranial neoplasms encompass a range of benign and malignant tumors arising from the brain parenchyma and its adjacent structures. These neoformations are an important cause of morbidity and mortality in companion animals, especially in dogs (Kishimoto *et al.*, 2020). Gliomas are the second most common primary intracranial tumor found in dogs and are highly prevalent in brachycephalic dogs, including English bulldog, French bulldog, and boxer dogs (Miller; Miller; Rossmeisl, 2019). Glial cell tumors include oligodendrogliomas, astrocytomas, and undifferentiated gliomas, which tend to occupy the intra-axial region (Koehler *et al.*, 2018).

Epidemiological data on gliomas indicate predisposition in terms of age, on average eight years, affecting mainly male dogs, and are predominantly located in the frontal, olfactory, temporal, and parietal lobes of the brain. The clinical presentation varies according to the location of the tumor (José-López *et al.*, 2021).

Imaging diagnostic modalities are essential tools to identify mass growth. However, they are insufficient to obtain a definitive diagnosis of most intracranial neoplasms in routine veterinary neurology.

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Given current limitations, the acquisition of representative samples of brain tissue would be an alternative, although not always feasible, for requiring histopathological examination. Such conduct aims at the definitive diagnosis to guide the best clinical management (Kani *et al*., 2019).

This work aims to report a case of astrocytoma in a French bulldog, demonstrating a longer survival time with conservative treatment compared to that described in the literature. Furthermore, it highlights the challenge in relation to the definitive diagnosis of intracranial neoformations in small animals.

## CASE REPORT

In 2021, a spayed French bulldog, seven years old, weighing 12.0 kg, was seen at a private veterinary clinic in the city of Goiânia – Goiás, with a history of cluster epileptic seizures that occurred over five days prior to neurological consultation. On the day the epileptic seizures occurred, the owner took the animal to emergency care where midazolam 0.3 mg kg IM and phenobarbital 2 mg kg IV were administered, which were effective in stopping the seizures. On the same day, phenobarbital (2.0 mg/kg, PO, BID, continuous use) was prescribed to the animal.

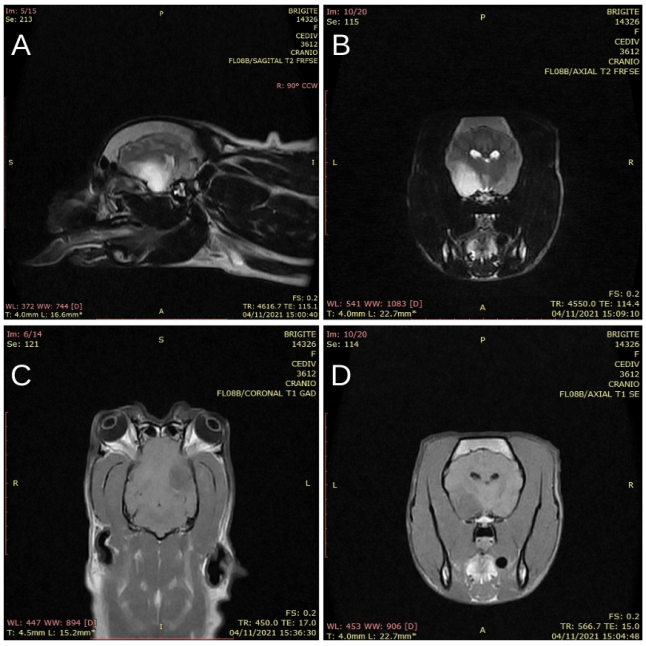
On the day of the neurological consultation, the animal did not present post-ictus effects but was already under the administration of phenobarbital. In the neurological evaluation, the animal showed an alert state of consciousness, normal behavior, normal posture, ambulatory gait, and no involuntary movements. There was a decrease in nasal sensitivity on the left side, but other tests of the cranial nerve pairs showed no changes. When evaluating postural reactions, proprioception was reduced in all four limbs, both in jumping and paw positioning tests. Spinal reflexes, muscle size, and perception of superficial and deep pain were normal. Furthermore, the evaluation revealed mild cervical hyperpathia. Based on the neurological evaluation, review, and patient history, clinical neurolocalization was performed, which indicated the prosencephalic region as possibly affected.

The clinical suspicions raised were based on the acromion DINAMIT V (Degenerative, Inflammatory/ Immune-mediated, Neoplastic/Nutritional, Anomalous, Metabolic, Idiopathic, or vascular diseases) commonly used in routine neurological investigation of small animals. Within these possibilities, the main suspicions included infectious, inflammatory, or neoplastic diseases. Additional tests were therefore recommended for investigation. We then requested serum phenobarbital dosage tests, cranioencephalic and cervical resonance, CSF collection for physical-chemical analysis and a multiplex PCR panel to investigate infectious diseases, in addition to a qualitative PCR for distemper, which was not included in the panel.

The qualitative PCR for distemper did not detect the presence of the distemper virus (Canine Distemper Virus) in the sample studied. The cerebrospinal fluid analysis indicated that the pH (7.0) was below the reference value and the cerebrospinal fluid glucose (65.9 mg/dL) was slightly above the reference value. On the other hand, chlorides (102.1) were slightly decreased. According to laboratory reference values, Pandy's reaction was positive (+/4+). The protein was within normal limits (27mg/dL). On microscopic examination there was a marked presence of red blood cells (772 cells/mm3), and leukocyte cells (5 cells/mm3), where 100% of these were lymphocytes. A real-time qualitative PCR was performed for the detection of canine infectious agents *Anaplasma* spp., *Ehrlichia* spp., *Trypanosoma* spp., *Leishmania* spp., *Neospora caninum, Blastomyces dermatitidis, Cryptococcus* spp., *Bartonella* spp., *Brucella* spp., *Histoplasma capsulatum, Hepatozoon* spp., *Rickettsia* spp., *Babesia* spp., *Toxoplasma gondii, Leptospira* spp., but none of the agents were detected in the sample. Bacilloscopy, verified using the Ziehl Neelsen technique, did not find acid-fast bacilli. The research on fungi, Chinese ink, did not show blastoconidia or capsulated yeasts typical of *Cryptococcus* spp. in the sample. The direct examination for fungi did not reveal a fungal sample. Bacterioscopy did not visualize Gram-stainable structures.

The MRI report showed a slightly rounded intra-axial formation (Figure 1) with partially defined limits, markedly hyperintense on T2-weighted sequences, slightly hyperintense on FLAIR and slightly hypointense on T1, measuring approximately 2.4 cm in diameter. The lesion did not capture paramagnetic contrast and presented a moderate local mass effect, centered in the left ventral parieto-temporal region, causing slight compression of the left thalamus and left lateral ventricle, as well as a slight deviation to the right of the midline (Falx). The main differential diagnosis included an intra-axial neoplastic process such as glioma. Among the other changes shown on MRI, mild bilateral otitis, moderate C2 syringomyelia, disc protrusion without spinal cord compression between C2-3 and dehydration, and multifocal disc degeneration were observed.

**Figure 1 –** Brain MRI of a French bulldog with a history of seizures where it is possible to observe intra-axial formation. A) Sagittal view in T2-weighted, markedly hyperintense formation. B) Transverse view in T2-weighted, markedly hyperintense formation intra-axial lesion in the left ventral parieto-temporal region. C) Dorsal view, T1 weighted, slightly hypointense formation. D) Transverse view, T1- weighted, slightly hypointense formation.




Source: Authors' own collection.

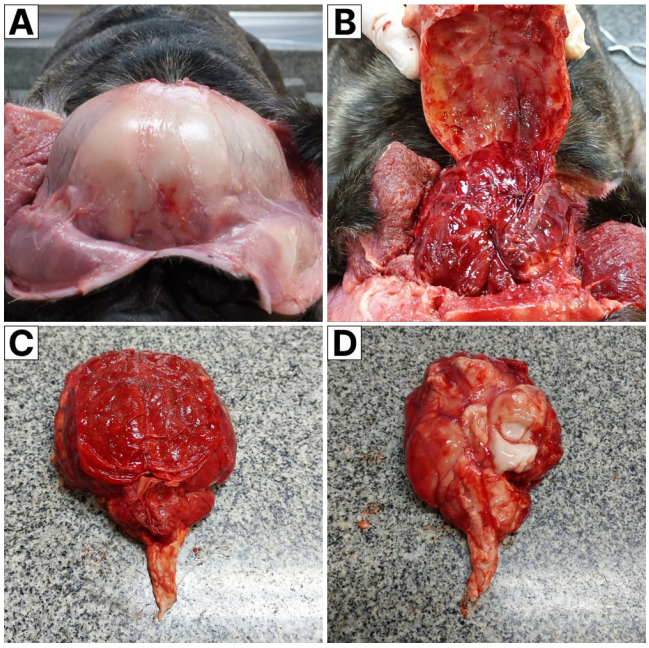
Two weeks after the first clinical appointment, the owner returned to the clinic with the animal for a follow-up and serum phenobarbital dosage after 15 days of medication administration. The serum level of phenobarbital was close to the minimum reference value of 16 mcg/mL. However, as the patient did not present any more crises, the same dose of the drug was maintained and it was clarified that if the patient presented new crises, the dose would be adjusted, and a new serum measurement would be carried out. Upon evaluation, the patient was clinically well, but still had a slight proprioceptive deficit in the four limbs, which was more evident in the pelvic limbs (PM), mild cervical hyperpathia, decreased menace response in the left eye alongside decreased left nasal sensitivity. With the results of the exams, it was possible to discuss clinical conduct with the tutor, explaining all the diagnostic possibilities that included the possibility of biopsy guided by neuronavigation or even an attempt at surgical resection with the aid of an ultrasonic aspirator and neuronavigation technology. Furthermore, the possibility of empirical and palliative non-surgical treatments was also discussed with the tutor. The treatments suggested included radiotherapy, chemotherapy, or corticosteroid therapy for symptomatic control, with main action on vasogenic edema, in addition to analgesia protocols. Based on all the possibilities, the refused surgical intervention, due to the risks inherent in the techniques and also did not accept empirical treatments such as radiotherapy, chemotherapy, and corticosteroid therapy. Therefore, therapy with gabapentin (5mg/kg/continuous use) was initiated.

After 37 days of the only cluster episode presented by the animal, which was in October 2021, the patient showed a new cluster episode with three self-limiting epileptic seizures spaced within a 24-hour interval. The phenobarbital dose was then readjusted to 3mg/kg. After fifteen days of administration of the phenobarbital new dose, a new serum measurement of phenobarbital was performed. In this measurement, the serum concentration, 23 mcg/mL, was higher when compared to the previous one.

The patient remained stable and seizure-free until January 2022, when the animal presented two epileptic seizures on the 18$^{th}$ and 19$^{th}$, and subsequently four epileptic seizures in March 2022, two focal and two generalized, on the 24$^{th}$ and 25$^{th}$, therefore, the phenobarbital was readjusted to 75 mg (5.5 mg/kg), BID. Five months after the diagnosis, due to the reduction in the interval between attacks, the tutor again reinforced the therapeutic possibilities and started corticosteroid therapy. Treatment from this moment on was maintained with phenobarbital, together with symptomatic treatment, prednisolone 5mg (0.5 mg/kg), SID and gabapentin (5mg/kg) TID. The prognosis was considered guarded, but despite the crises, the patient remained well clinically. Blood and biochemistry profile was performed approximately every 60 days. In May 2022, 218 days, that is, approximately 31 weeks after diagnosis, the patient suddenly presented a reduced state of consciousness, which progressed to stupor and death within a period of 48 hours.

At necropsy, the brain exhibited a reddish discoloration, with a whitish neoformation on the left ventral portion, corresponding to the lesion identified on MRI (Figure 2). Histopathological evaluation revealed an infiltrative, moderately cellular, unencapsulated, and poorly demarcated neoformation extending into adjacent brain structures. Microscopically, the lesion consisted of polyhedral, fusiform to stellate neoplastic cells with astrocytic morphology, arranged in loose bundles, cords, or rows within a moderate amount of loose neuropil, interspersed with frequent capillary vessels. The neoplastic cells exhibited scant, acidophilic, poorly defined, homogeneous cytoplasm, and round to oval, uniform nuclei with fine chromatin and inconspicuous nucleoli. Mild anisocytosis, anisokaryosis, and cellular pleomorphism were observed, without areas of necrosis or mitotic figures in the analyzed 2.37 mm$^2$ field. Based on microscopic findings, the final diagnosis was consistent with a diffuse astrocytoma.

**Figure 2 –** Image from the necropsy performed on a French bulldog with suspected Glioma. A) Brain with frontal hemorrhage point. B) Diffuse reddish areas in the brain. C) Dorsal view of edematous and hemorrhagic brain. D) Intra-axial mass in the left ventral parieto-temporal region.




Source: Authors' own collection.

The patient in this report is a French bulldog diagnosed with glioma, subclassified as astrocytoma. Approximately 90% of primary brain tumors (TCP) found in veterinary clinical practice are represented by meningiomas, gliomas, which include astrocytoma in this classification, and, to a lesser extent, choroid plexus tumors (Miller; Miller; Rossmeisl, 2019). It seems relevant to emphasize that glioma represents 20% to 40% of primary intracranial tumors in dogs, and certain brachycephalic breeds, including Boxers, Bulldogs, and Boston Terriers, have been reported to be at high risk of developing these tumors (Narita *et al.*, 2020).

The epileptic seizure was the main clinical manifestation presented in this report. Clinical history and presenting signs for animals with intracranial neoplasia may vary and reflect consequences of both the primary tumor site and its secondary effects (Schwartz *et al.*, 2011). The most common clinical presentation includes epileptic seizures, abnormal mental status, gait abnormalities, cranial nerve deficits,

proprioceptive deficits, posture abnormalities, and neuropathic pain (Moirano *et al*., 2018).

CSF analysis often provides complementary data for clinical examination and diagnostic imaging results. Furthermore, even though CSF is a sensitive indicator of intracranial disease and is frequently abnormal in patients with brain tumors, leukocyte counts, and total protein concentrations are highly variable and not specific for neoplasia (Miller; Miller; Rossmeisl, 2019). Although the exam does not provide specific information for the diagnosis of intracranial neoplasms, it is an excellent tool that helps to exclude inflammatory and infectious causes of brain dysfunction (Andrade Neto *et al*., 2015). Consistent with the findings of the report, despite the non-specific result, CSF was a fundamental tool in excluding other CNS disorders.

Computed tomography (CT) and MRI images are currently the most used exams to evaluate intracranial diseases. MRI provides the best chance of detecting brain mass and characterizing it due to its extreme sensitivity to soft tissue (Miller; Miller; Rossmeisl, 2019). The MRI findings regarding intra-axial formation demonstrate the same pattern presented in the literature to describe the pattern of gliomas, since the majority present signal intensities, and are generally T1-weighted hypointense and T2 hyperintense, but mixed intensities, particularly in FLAIR, it is worth highlighting that glioma presents mass effect in approximately 90% of cases, as shown in the patient's MRI (Bentley, 2015).

Given the limitations of diagnostic imaging, acquiring representative brain tissue samples is the only way to obtain a definitive antemortem diagnosis (Kani *et al*., 2019). Biopsy is not always performed due to the cost and morbidity of the animals, but nowadays there is a range of methods described, such as stereotactic CT-guided biopsy (Andrade *et al.*, 2015).

The definitive diagnosis of intracranial tumors is based on histopathological evaluation using the World Health Organization (WHO) classification system (Dickinson, 2014). CT and MRI, in conjunction with pathological examination of biopsy specimens, have increased the accuracy of antemortem diagnoses of canine intracranial tumors in recent years (Kishimoto *et al*., 2020; Koehler *et al*., 2018; Miller; Miller; Rossmeisl, 2019). As seen in this case, the MRI performed was effective in proving the presence of intracranial neoformation, and in suggesting the possible tumor type. Histopathological evaluation confirmed a diffuse, infiltrative, unencapsulated, and poorly demarcated astrocytic neoplasm, characterized by moderate cellularity, mild pleomorphism, and absence of necrosis or mitotic figures, which was consistent with diffuse astrocytoma and corroborated the imaging findings.

Canine gliomas may be managed with symptomatic therapy, chemotherapy, radiotherapy, and, less frequently, surgery. Chemotherapy with temozolomide or lomustine shows limited and variable efficacy, with no standardized protocol (José-López, 2023). Stereotactic radiation therapy (SRT) offers median survival of 12 months and clinical improvement in 91% of cases (Trageser *et al*., 2023), while fractionated megavoltage radiotherapy achieves median survival of 698 days and 1- and 2-year survival rates of 74.2% and 49.0%, respectively (Debreuque *et al*., 2020). Laser Interstitial Thermal Therapy (LITT), though novel, has shown potential for tumor ablation, transient blood-brain barrier disruption, and synergy with immunotherapies (Wachsmuth *et al.*, 2023; Mariani *et al*., 2023). Surgical excision remains the least indicated option due to the infiltrative nature of gliomas and indistinct tumor margins (Hidalgo Crespo *et al*., 2022).

Conservative treatment through palliative care aims to improve the animal's quality of life. Furthermore, in this report, survival of 218 days with quality of life demonstrated a beneficial result, given that in the literature, survival after palliative care is approximately nine weeks, with an interval of one to thirteen weeks (Miller; Miller; Rossmeisl, 2019). Some studies have reported much lower average survival rates, such as the study that demonstrated average survival of 35 days in dogs with symptomatic treatment (Moirano *et al.*, 2018), and another with 60 days also with symptomatic treatment (Van Meervenne *et al*., 2014).

Despite the different treatment modalities for gliomas, no gold standard protocol has been recognized (Moirano *et al*., 2018). Furthermore, data evaluating the effectiveness of treatments used for brain tumors in dogs are significantly limited by the lack of definitive diagnosis in many of the reported cases (Miller; Miller; Rossmeisl, 2019).

## CONCLUSIONS

Despite the description of different therapeutic protocols and survival times, the patient in this report remained clinically well for 155 days with the use of phenobarbital alone and a further 63 days with the combination with prednisolone. Therefore, it is believed that more studies are needed to understand the real impact of different treatments on the quality of life and survival of patients with glioma. Furthermore, it is encouraged to obtain samples for antemortem histopathological examination, using either biopsies or surgical resections, as the lack of definitive diagnosis influences the proper choice of treatment.

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