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Case Report - Veterinary Medicine

Primitive neuroectodermal tumor in the cervical spine of a dog – Case Report

[*Tumor neuroectodérmico primitivo na coluna cervical de um cão – Relato de Caso*]

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ABSTRACT

A case of peripheral primitive neuroectodermal tumor in the cervical region of a canine is described. The patient was a canine, male, five years old, large size, with acute neurological clinical signs, severe neck pain and tetraplegia. On computed tomography, an oval-shaped mass located dorsally to cervical vertebrae C4 to C7 was observed, with infiltration over the spinal cord between vertebrae C4 and C5, discreetly widening the dorsal intervertebral foramina of the cervical vertebrae and compressing the dorsal portion of the spinal cord of this segment. Under microscopy, the neoplastic cells were small, irregular in shape and with scarce cytoplasm. Immunoreactivity for vimentin, which can only be expressed in PTNEs tumors, was decisive for diagnostic confirmation. Additionally, the positivity of the S-100 protein, which is expressed in neuroectodermal cells mainly of the neural crest cells, reinforced the classification as PTNE, and the negativity in the expression for glial fibrillary acidic protein (GFAP) ruled out the presence of small cell glioma of the central nervous system. Based on the clinical history, imaging exams, cellular morphology and mainly on immunohistochemical staining, the diagnosis of primitive neuroectodermal tumor (PTNE) with infiltration and compression of the spinal cord in the cervical region of the dog was confirmed, considered uncommon in this species.

Keywords: central primitive neuroectodermal tumor, peripheral primitive neuroendocrine tumor, dog

RESUMO

Descreve-se um caso de tumor neuroectodérmico primitivo periférico na região cervical de um canino. O paciente em questão era um canino, macho, de cinco anos, porte grande, com sinais clínicos neurológicos agudos, cervicoalgia severa e tetraplegia. Na tomografia computadorizada, foi observada uma massa de aspecto ovalado localizada dorsalmente às vértebras cervicais C4 a C7, com infiltração sobre a medula espinhal entre as vértebras C4 e C5, alargando discretamente os forames intervertebrais dorsais das vértebras cervicais e comprimindo a porção dorsal da medula espinhal deste segmento. Na microscopia, as células neoplásicas eram pequenas, de formato irregular e citoplasma escasso. A imunorreatividade para vimentina, que só pode ser expressa em tumores PTNEs, foi determinante para a confirmação diagnóstica. Adicionalmente, a positividade da proteína S-100, que é expressa em células neuroectodérmicas principalmente das células da crista neural, reforçou a classificação como PTNE, e a negatividade na expressão para proteína ácida fibrilar glial (GFAP) descartou a presença de glioma de pequenas células do sistema nervoso central. Com base no histórico clínico, em exames de imagem, na morfologia celular e principalmente na coloração imuno-histoquímica, confirmou-se o diagnóstico de tumor neuroectodérmico primitivo (PTNE) com infiltração e compressão na medula espinhal na região cervical do cão, considerado incomum nessa espécie.

Palavras-chave: tumor neuroectodérmico primitivo central, tumor neuroendócrino primitivo periférico, cão

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INTRODUCTION

A wide variety of embryonic tumors of the central nervous system, commonly malignant, are described in humans and animals (Berrocal *et al.*, 2005). However, primitive neuroectodermal tumors (PTNE) are undifferentiated embryonic tumors characterized by small, round, malignant cells that arise in soft tissue and bones. In humans, PTNE typically occurs in children and young adults (Berrocal *et al.*, 2005). Depending on their location, they are classified into central (cPTNE), which usually originate from the cerebellum, with spinal cord involvement being rare, or peripheral (pPTNE), which originate from the neural crest, arising from intraosseous neural tissue or soft tissues (Headley *et al.*, 2009).

In animals, most of the cases described are of central origin, with reports in cattle (Berrocal *et al.*, 2005), dogs (Snyder *et al.*, 2006; Choi *et al.*, 2012), cats (Kitagawa *et al.*, 2003) and non-human primates (Johnson *et al.*, 1999). Central PTNE accounts for 2.8% of primary intracranial neoplasms diagnosed in dogs (Snyder *et al.*, 2006; Hespel *et al.*, 2021). Peripheral PTNE are considered uncommon, being difficult to find reports in the literature, and the last ones described were located in the thoracic and lumbar regions of dogs (Snyder *et al.*, 2006; Junginger *et al.*, 2013; Hespel *et al.*, 2021).

Clinical signs are variable and often nonspecific, and their manifestation depends on the location where the tumor is installed and the expansion of the lesion (Nery *et al.*, 2018). In humans with pPTNE in the cervical spine, it is common to report pain, encephalitis, severe and progressive neck pain, hyperextension of the cervical muscles, with dissociation of temperature and proprioception, and, substantially, hemiparesis, tetraparesis or tetraplegia (Cabral *et al.*, 2012). cPTNE differs from pPTNE by the presentation of seizures and cranial signs, which does not happen in pPTNE (Nery *et al.*, 2018). In pPTNE, it is common for primary foci to start in the paravertebral, pelvic, or thoracic wall regions; however, there are descriptions in humans of cases in the bladder, rectum, myocardium, nasal cavity, and retroperitoneum (Facemire *et al.*, 2012). The sites of metastatic predilection are the lung, pelvis, and spinal cord, due to the high vascularity of these sites, with abdominal ultrasound and thoracic and pelvic radiographs being important allies for the search for tumor metastases (Tiago *et al.*, 2007).

Imaging diagnostic techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) are relevant despite the findings being considered non-specific, as CT helps in the evaluation of adjacent tissues and metastases and MRI provides information on the delimitation of the mass, abnormal tissues, and their relationship with adjacent nervous and vascular structures (Ibarburen *et al.*, 1996; Cabral *et al.*, 2012).

The definitive diagnosis for PTNE requires histological and immunohistochemical analysis, and more recently cytogenetic study is advocated (Feng *et al.*, 2021). Microscopic analysis reveals small round cells, rounded, oval and/or fusiform nucleus, scarce cytoplasm with numerous degrees of mitosis, being a well-defined mass, white to yellow in color (Wick, 2000; Lucas *et al.*, 2003). Sometimes it can present the formation of neuroblastic rosettes (Homer-Wright). Due to the histological similarity of neoplasms of embryonic origin with those of primitive neuroectodermal origin in humans and animals, only immunohistochemistry can point out a variety of neuroectodermal, ependymal, glial and, mainly, neuronal cellular dissimilarities (Berrocal *et al.*, 2005). From the perspective of immunoreactivity, depending on the degree of differentiation, cells can be positive for glial or neural markers, such as glial fibrillar acid (GFAP), synaptophin, vimentidine and S-100 protein (Hespel *et al.*, 2021). Because this neoplastic diagnosis is uncommon in veterinary medicine, we decided to report the present case of a primitive neuroectodermal tumor in the cervical region with infiltration and compression of the spinal cord in a dog.

CASUISTRY

A male canine, five years old, mixed-breed, and with large size, was admitted to the neurology sector of the veterinary hospital of the Federal University of Mato Grosso (UFMT) located in Cuiabá, Mato Grosso, with a history of staggering gait, pain when standing up and position of prayer for ten days with evolution to tetraplegia the day before the veterinary care. Feeding was based on dry and wet food, with no information on homemade food intake.

On physical examination, the body score was classified as "5" (1-9) and the physiological parameters were within normal limits, with only a degree of dehydration of 6-8%. Neurological evaluation indicated alert mental status, normal cranial nerves, tetraplegia with increased muscle tone, and no withdrawal reflex in the thoracic limbs. In the pelvic limbs, muscle tone was within normal limits, the patellar reflex was increased, presence of withdrawal reflex but absence of conscious proprioception, with stimulation of superficial and deep pain preserved in the four limbs. Additionally, during epaxial palpation, there was no evidence of volume increase, but hyperextension and severe neck pain were detected when moving the neck.

In view of the history and clinical presentation, cervical syndrome of neoplastic origin was suspected, and to conclude the etiological diagnosis, the following exams were requested: complete blood count, dosage of total serum proteins and albumin, dosage of serum enzymes alanine amino transferase, alkaline phosphatase and creatinine, and hemostatic profile (prothrombin time and activated partial thromboplastin), and the values obtained were within the normal range for the species.

Additionally, imaging exams were performed. Radiographs of the thoracic region in laterolateral projection and of the pelvic region in ventrodorsal projection, in addition to abdominal ultrasonography, did not show alterations. Simple helical scan computed tomography of the cervical spine at a 2mm slice thickness showed a mass of approximately 5.8 × 5.2 × 6.6cm (Length × Height × Width), oval in appearance, homogeneous and slightly hypodense in relation to the adjacent musculature (Fig. 1), located dorsally to the cervical vertebrae C4 to C7. The mass infiltrated with greater intensity over the spinal cord in the segment of the cervical vertebrae C4-C5 and discreetly projected the dorsal intervertebral foramina of the cervical vertebrae, compressing the dorsal portion of the spinal cord (Fig. 1).

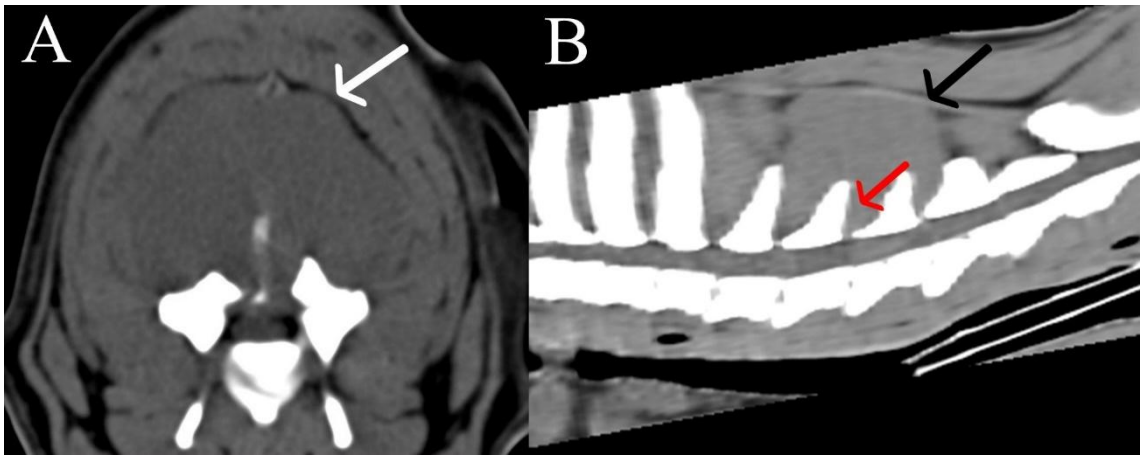

Figure 1. Computed tomography images of the cervical region of a canine, mixed-breed, large size and with five years old. A) Mass with an oval appearance, homogeneous, slightly hypodense in relation to the adjacent musculature, measuring approximately 5.8 × 5.2 × 6.6cm (white arrow). B) Mass located dorsally to cervical vertebrae C4 to C7 (black arrow). The mass infiltrates with greater intensity over the spinal cord between the C4 and C5 vertebrae, discreetly widening the dorsal intervertebral foramina of the cervical vertebrae and compressing the dorsal portion of the spinal cord of this segment (red arrow).

For differential diagnosis, polymerase chain reaction (PCR) was performed for *Ehrlichia canis*, *Babesia* spp., *Trypanosoma cruzi* and *Leishmania infantum* and serology for *Toxoplasma gondii* and *Neospora caninum* by indirect immunofluorescence reaction (IFA), all with negative results.

On the first day of care, the dog was hospitalized and instituted as a therapeutic protocol fluid therapy with Ringer's solution with Lactate 20ml/kg/hour, gabapentin 10mg/kg, carprofen 2.2mg/kg and tramadol hydrochloride 3mg/kg, all every twelve hours for pain control, in addition to multivitamin compound (vitamin B

0.2ml/kg and vitamin C 30mg/kg, both every twenty-four hours), massage of the four limbs, change of decubitus every two hours, cold compresses in the cervical region and measurement of blood pressure every twelve hours. Blood pressure remained within normal limits during the hospitalization period. On the third day, the canine presented difficulty in apprehending food due to pain and cervical hyperextension, so feeding management was instituted with the patient in sternal recumbency. On the fourth day, a progression of the neurological condition was observed, and sulfamethoxazole was added to the therapy associated with trimethoprim at a dose of 15mg/kg every twelve hours and clindamycin at the same dose, and prednisolone 2mg/kg every twelve hours in case of suspected infection and/or inflammation of the central nervous system, in addition to carprofen withdrawal. After six days of hospitalization, the patient presented a significant worsening of the clinical condition, with a decrease in muscle tone and atrophy of the bilateral cervical muscles and thoracic limbs, urinary and fecal retention, worsening in the apprehension of food and neck pain, in addition to progressive weight loss.

Due to the extension of the mass in the cervical region, surgical complexity and worsening of the clinical evolution of the canine, the owner chose to perform euthanasia and subsequent necropsy.

At necropsy, the macroscopic evaluation showed a white mass, measuring 5.5 × 5.0 × 4.5cm, firm to palpation, in the dorsal cervical region (Fig. 2), where invasion and replacement of the cervical muscles by the tumor was observed, in addition to infiltration in the body of cervical vertebrae C4 to C6, mainly in C5 (Fig. 2), with compression of the spinal cord. In the microscopic analysis, the nodule was delimited by trabeculae and fibrous tissue, with a delimited and expansive lobular aspect with multifocal areas of infiltration in the skeletal muscle tissue, generating atrophy and necrosis.

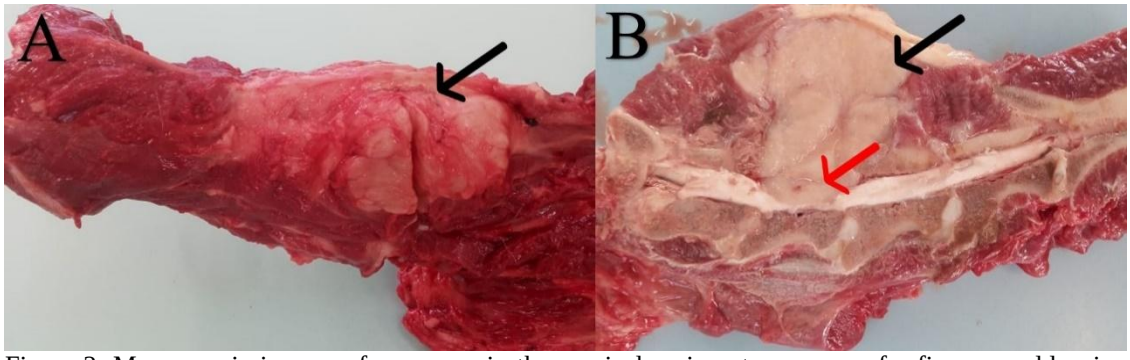

Figure 2. Macroscopic images of one mass in the cervical region at necropsy of a five-year-old, mixed breed dog of large size. A) Mass in the cervical region with white color, interspersing and replacing the bilateral cervical cleidocephalic muscles, measuring 5.5 × 5.0 × 4.5cm (arrow). B) Cut surface of the mass showing good delimitation of the tumor invading the cervical musculature (black arrow), as well as infiltrating the body of cervical vertebrae C4 to C6 and compressing the spinal cord mainly in the cervical vertebral segment C5 (red arrow).

Neoplastic proliferation showed a pattern of nest of cells, sometimes forming bundles. The cells exhibited a high degree of pleomorphism and anaplasia. They predominantly had a polygonal format, and to a lesser extent fusiform, and exhibited scarce cytoplasm, with inconspicuous borders and a high ratio between nucleus and cytoplasm (Fig. 3). The nucleus was round to oval with finely punctuated to marginated chromatin next to the nuclear membrane, with a light coloration and having a nucleolus. There are four to six mitotic figures per high-power field. They had marked anisocytosis and anisokaryosis. Polygonal cells had intercellular connections with neighboring cells (Fig. 3).

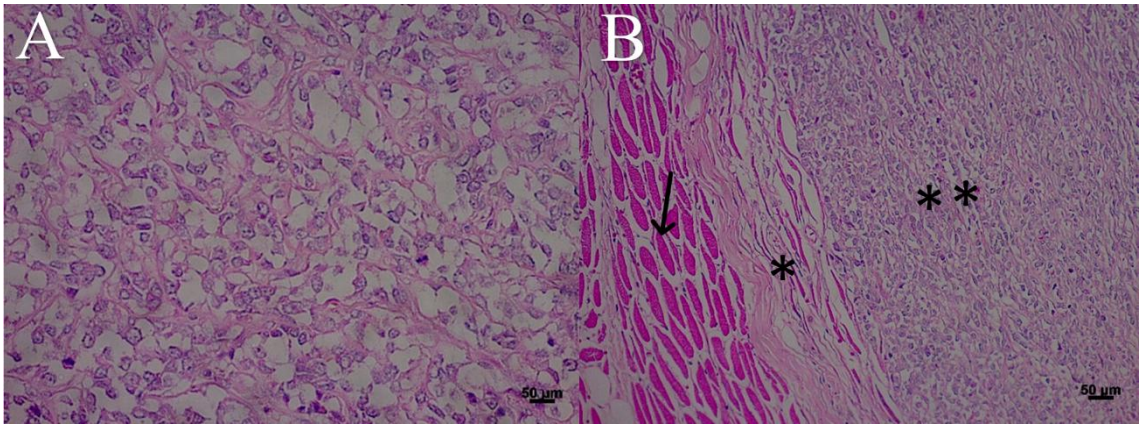

Figure 3. Male dog, no defined breed with five-year-old. A) Neoplastic cells with scarce or absent cytoplasm, clear nucleus and rounded and elongated shape, with marginated chromatin and anisokaryosis. HE. 40×. B) Cross section of the skeletal muscle fibers with an elongated shape (arrow), between the muscle cells and the neoplastic population, a muscle fascia (*) is observed. The neoplastic population demonstrated a distribution in bundles (**). HE. 20×.

For immunohistochemical analysis and in the investigation of reactivity to epithelial tumors, a marker for pancytokeratin (AE1/AE3) was used, with a negative result. The vimentin marker for mesenchymal tumors was used, which scored 20% positive. For muscular tumors, actin-α and desmin were used, both being negative. Based on this result, a tumor originating from the nervous system was suspected, and the markers were used for diagnostic confirmation, such as synaptophysin (Fig. 4), where 60% of the cytoplasm in tumor cells was reactive, S-100 protein (Fig. 4) with 50% positivity for cell cytoplasm and finally GFAP with no staining. Due to the histological and immunohistochemical characteristics, the diagnosis of a primitive neuroectodermal tumor was suggested.

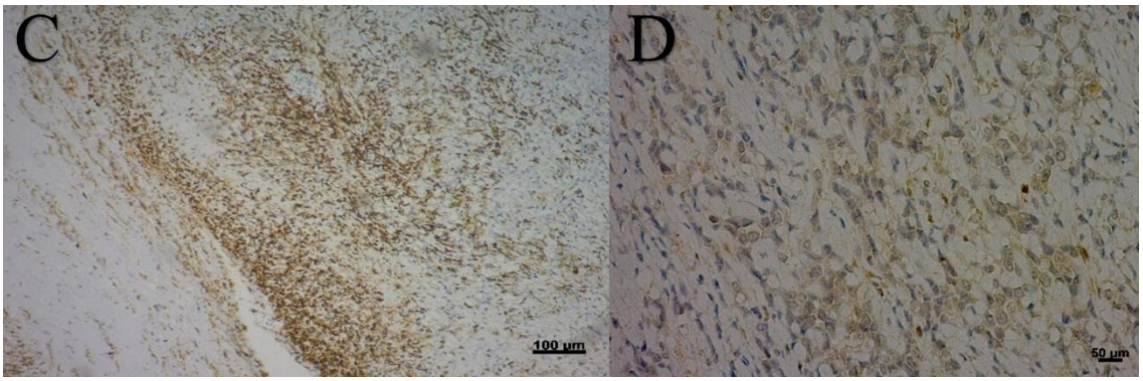

Figure 4. Immunohistochemical analysis of the primitive neuroectodermal tumor in the cervical spine of a five-year-old, mixed breed dog. C) Intense staining of tumor cells with synaptophysin staining. Immunohistochemistry. HE. 10×. D) Positive staining in the cytoplasm in immunohistochemistry for S-100 protein in neoplastic cells. 40×.

DISCUSSION

Primitive neuroectodermal tumors (PTNE), as in the case presented, are considered to be anatomically atypical tumor growth in animals and humans, making it difficult to determine the point of origin of the tumor, however, since there was no bone abnormality in the macroscopic examination, it is likely that the site of origin of this tumor is in some segment of the cervical spinal cord (such as a nerve root), which then invaded the dorsal cavity of the cervical musculature, a similar characteristic to what was described in a case of pPTNE in the cervical

region of a woman and in the thoracolumbar region of a dog (Cabral *et al.*, 2012; Hespel *et al.*, 2021).

Tumors of central primitive neuroectodermal origin of the brain parenchyma represent 2.8% of cases of dogs diagnosed with primary intracranial neoplasia (Snyder *et al.*, 2006; Hespel *et al.*, 2021). However, it is important to point out that regardless of whether the tumor is of central or peripheral origin, this type of tumor affecting the cervical region of dogs as described in this case is extremely uncommon, with reports only being found in humans; and the last cases described in dogs affected the thoracolumbar region (Junginger *et al.*, 2013; Hespel *et al.*, 2021).

There is no pathognomonic sign at clinical presentation, and clinical signs will depend on the affected site and the degree of invasion (Hespel *et al.*, 2021). In general, the neurological examinations of this patient were consistent with myelopathy in the cervical region, due to increased muscle tone in the thoracic limbs, lack of conscious proprioception, increased patellar reflex, absence of seizures and cranial nerve alterations, hyperextension of the cervical musculature, severe neck pain and progression of systemic clinical signs, such as urinary and fecal incontinence (Cabral *et al.*, 2012). However, the alterations observed in the canine of this report are consistent with those described in the pPTNE and cervicomedullary PTNE in humans, such as tetraplegia, cervical hyperextension, and severe neck pain, and differing from the cPTNE because there are no cranial signs and seizures (Nery *et al.*, 2018). The fact that the canine does not show cranial nerve deficits and seizures is one of the clinical factors that supports the hypothesis that this neoplasm is a PTNE of peripheral origin based on the report by Hespel *et al.* (2021).

Although it is a neoplasm recognized for its aggressiveness with a high rate of metastasis in humans, no metastasis was observed in this patient, considering that the imaging exams of the thoracic, pelvic, and abdominal regions were normal (Tiago *et al.*, 2007). Despite this, computed tomography showed a mass in the cervical musculature with expansion in the medullary region between the C2-C5 vertebrae. It is likely that the tumor was developing over the years, and due to compression in this region, the clinical signs of this dog began.

This patient was submitted to a computed tomography exam due to the impossibility of performing the magnetic resonance, and even with the low sensitivity of the tomography in relation to the resonance, a large well-defined mass was observed in the cervical region invaginating the adjacent and intramedullary muscles, mainly in the C5 cervical vertebra, similar to the description of a case in a man in 2013 (Nery *et al.*, 2018). Additionally, the tumor with a homogeneous and slightly hypodense appearance compared to the adjacent tissues was visualized, which penetrated the cervical spinal cord, equivalent to the case described in a child in 2012 with an intramedullary primitive neuroectodermal tumor in the cervical region (Alexiou *et al.*, 2013). These CT findings are suggestive of cPTNE and pPTNE, as well as rhabdomyosarcoma, medulloblastoma, lymphoma, nerve sheath tumors, and carcinoma (Nery *et al.*, 2018).

The microscopic characteristics found in the tumor, such as small, oval cells, with little cytoplasm, high rate of mitosis and undifferentiated, in addition to the slightly elongated and irregularly shaped nuclei and cytoplasm, and the isolated infiltration of neoplastic cells in the adjacent tissue are similar to those described in cattle with PTNE (Lucas *et al.*, 2003) and very similar to the cell morphology found in this report, in addition to being clear the visualization of the neoplasm developing in isolation and at the same time expanding and compressing the adjacent muscle cells. These characteristics, combined with the macroscopic characteristics of a well-delimited, white tumor, with a presentation of necrosis similar to that described by Argenta *et al.* (2018) maintain that it is a neoplasm of PTNE origin. As mentioned by other authors, the immunohistochemical evaluation was able to characterize the neoplasia that affected the canine in this report. The absence of immunoreactivity for desmin, actin-α and monoclonal antibodies developed against the human epidermis AE1/AE3 ruled out the presence of rhabdomyosarcoma and epithelial tumors, such as carcinomas and meningiomas, as commonly in the latter the parts that surround it are positive for AE1/AE3.

Immunoreactivity for synaptophin may be present in neuroendocrine and neuroectodermal tumors, however, in the present report, positivity for vimentin was crucial for diagnostic confirmation, as this immunostaining can only be expressed in PTNEs tumors. Additionally, the positivity of the S-100 protein, which is expressed in neuroectodermal cells mainly of the neural crest cells, reinforced the classification as PTNE (Berrocal *et al.*, 2005; Cabral *et al.*, 2012), and the negative expression for glial fibrillary acidic protein (GFAP) ruled out the presence of small cell glioma of the central nervous system (Berrocal *et al.*, 2005; Hespel *et al.*, 2021). In addition to immunohistochemistry, which determined it to be a PTNE tumor, other factors that may suggest classifying this case as pPTNE is the fact that no involvement of the cervical vertebrae and brain was detected at necropsy, and the clinical presentation did not show any cranial nerve involvement, which differs from "Ewin's Sarcoma" and cPTNE (Berrocal *et al.*, 2005). The diagnosis of primitive neuroectodermal tumor (PTNE) was based on clinical history, imaging exams, cellular morphology and mainly on immunohistochemical staining, not being possible to perform tumor cytogenetics or to determine whether the neoplasm developed from the central or peripheral spinal cord segment. Based on the case described by Hespel *et al.* (2021), some of the differential diagnoses for this mass include nerve root tumor, peripheral nerve sheath neoplasm and neuroblastoma.

In human cases of primitive ectodermal tumors, treatment consists of surgical removal of the neoplastic mass and chemotherapy or radiotherapy, which results in a five-year survival without tumor progression for 50%-60% of patients (Hespel *et al.*, 2021). In this case, due to the surgical complication and the clinical worsening of the animal, euthanasia was the option chosen by the owner.

CONCLUSION

Peripheral primitive neuroectodermal tumor (pPTNE) should be considered in the differential diagnosis in dogs with neurological dysfunction and apparent soft tissue mass in the cervical region and other regions of the spine, along with invasion of the spinal cord region. Computed tomography was an important tool for detecting the tumor mass and determining the animal's prognosis, but microscopic analysis and mainly immunohistochemistry were the conclusive methods of etiological diagnosis.

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