Lumbar Malignant Peripheral Nerve Sheath Tumor in a Young Dog

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ABSTRACT

Background: The most common location of malignant tumors of the peripheral nerve sheath in the spinal cord is the intradural-extramedullary region, and is rare in the spinal nerve roots in the lumbar region. They mainly affect large female dogs over 6 years of age. Imaging tests assist in the presumptive diagnosis, but confirmation requires histopathological and immunohistochemical examination. The prognosis is guarded. Diagnostic imaging, anatomopathological and immunohistochemical findings of a malignant tumor of the intradural-extramedullary peripheral nerve sheath with medullary infiltration in the lumbar region in a young dog are reported.

Case: A body of a 6-year-old Poodle dog was donated for necropsy and diagnostic clarification. In the history, there was a suspicion of lumbar intramedullary neoplasia, detected by computed tomography (CT), with a 4 years progressive chronic evolution. Additionally, the dog had hidden spina bifida (L7 to S3), as detected by radiography and CT. On *post mortem* radiographic examination (X-ray), there was an enlargement of the vertebral canal (T10 to S2), intense osteolysis (L1 to S2), spinous processes (L5 to L7), and ankylosis (L3 to L7). Necropsy revealed ankylosis (L3 to L7) and intradural-extramedullary mass ($9.5 \times 2.6 \times 2.3$ cm) (L2 to L6). No metastases were identified. On microscopy, there was neoplastic proliferation of cells with intense pleomorphism, arranged in bundles interlaced in palisades and sometimes solid mantles. The mitotic index was high, ranging from 10 to 12 mitoses per field. There was also necrosis, hemorrhage, edema, and focal axonal demyelination of the adjacent white matter in the spinal cord. Masson Trichrome staining highlighted an intense diffuse conjunctive stroma. There was a suspicion of a malignant tumor of the peripheral nerve sheath and an immunohistochemical panel was performed for confirmation. There was strong and diffuse positivity for vimentin and S-100 and partial positivity for neuron-specific enolase (NSE), negative for anti-factor VIII, glial fibrillary acidic protein (GFAP), α-actin for smooth muscle, cytokeratin, neurofilament, and desmin. Thus, the diagnosis of malignant neoplasm of the peripheral nerve sheath was confirmed.

Discussion: Peripheral nerve sheath tumors are classified as benign or malignant. In dogs, they are frequent in elderly, females, and large breeds. In this case report, the animal was young, female, and small breed. The location of the spinal nerve roots is uncommon, and is more commonly found in the brachial plexus. In the animal reported, the tumor was observed as lumbar swelling. Clinical signs vary with the affected region, however, neurogenic claudication and muscle atrophy are more frequent, as observed in this report. Imaging examinations such as X-rays and CT assist in the presumptive diagnosis. In this case report, spina bifida was identified on radiography, and CT suggested the presence of intramedullary neoplasia and allowed to monitor tumor growth. *Post mortem* X-ray imaging revealed intense osteolysis and ankylosis, which were confirmed at necropsy, which also elucidated its intradural-extramedullary location with infiltration into the spinal cord. The confirmation of the neoplasm was made by histopathological and immunohistochemical examination; the latter should be made a panel, not restricted to the use of antibodies S-100 and vimentin only. The prognosis of malignant peripheral nerve sheath tumors (MPNST) of the spinal cord is poor, and although there are palliative methods, there is no curative treatment, as complications can interfere with the quality of life of the animal. MPNST should be included in the differential diagnosis of spinal disorders, even in young dogs and small breeds. CT helps in early diagnosis to make decisions aimed at the animal's well-being.

Keywords: neoplasm, spinal cord, intradural-extramedullary, canine.

INTRODUCTION

Benign peripheral nerve sheath tumors (BPNST) or malignant peripheral nerve sheath tumors (MPNST) of the spinal cord can have an extramedullary, intradural-extramedullary, and intramedullary location [11,26]. They originate from the cranial and spinal nerves, mainly, peripheral nerves, and occasionally infiltrate the medullary canal and compress the spinal cord [2,22]. They mainly affect large breed female dogs over the age of six [2,4,14]. The prognosis is guarded and the clinical manifestation depends on the affected region; however, lameness of chronic neurogenic origin with consequent muscular atrophy of the limbs, is the most common sign [11,22]. Imaging tests such as radiography (X-ray), computed tomography (CT), and magnetic resonance imaging contribute to the presumptive diagnosis and detection of the tumor; however, the diagnostic confirmation depends on the histopathological evaluation and immunohistochemical panel, leading to differentiation with other neoplasia [4,16]. Imaging tests and anatomopathological and immunohistochemical findings of a malignant tumor of the intradural-extramedullary peripheral nerve sheath with marrow infiltration in the lumbar region in a young dog are reported.

CASE

A body of a 6-year-old female Poodle dog was donated to the Veterinary Pathology Laboratory (LPV) of the Veterinary Medicine Hospital (HOSPMEV) of the Federal University of Bahia (UFBA) for diagnostic clarification.

The clinical history was not complete, but it contained information that the dog had previously been seen by the veterinarian at the age of 2 years, with a complaint of lameness that progressed to paralysis of the hind limbs (HL) in two months. Blood count and biochemical examinations, radiographic examination with changes compatible with hidden spina bifida, and two CT exams of the lumbar spine and lumbosacral spine, performed in a private veterinary clinic, at an interval of 6 months showed similar results. Clinical examination revealed bladder distention, proprioceptive HL ataxia, and associated muscle atrophy, most evident in the right hindlimb (RHL), inability to walk, spinal reflexes absent in RHL, and reduced in the left HL. Conservative treatment with analgesia, physiotherapy, and environmental management in order to provide more comfort to the patient, in addition to quarterly clinical monitoring, was established. The animal remained stable in the following years, but at 6 years of age, there was a worsening of the condition with progression to tetraparesis, prostration, emesis, and death.

In CT examinations performed on four-channel helical equipment (Asteion[1]) of private service, the images were acquired in cross-sections with a thickness of 1 mm and with soft tissue and bone filters, pre - and post-injection of iodinated intravenous contrast. In the first CT examination, at 2 years of age, a hyper-attenuating area was observed in the spinal cord, at the height of L4 and L5, with poorly defined contours, which measured 1.1×0.4 cm in the sagittal plane and 1.1×0.6 cm in the dorsal plane. In the post-contrast phase, it was possible to identify a greater extent of the lesion (1.35×0.42 cm in the sagittal plane and 1.53×0.75 cm in the dorsal plane), in addition to discreet uptake of contrast in its periphery (Figure1A). The diagnostic conclusion of CT was an expansive neoplastic or inflammatory lumbar intramedullary process in addition to spina bifida, already identified in a previous radiographic examination. Six months after the first examination, a second control CT was performed, in which the non-contrast phase identified spinal cord enlargement with poorly defined contours, which extended from the middle caudal third of L3 to the cranial third of L5, with approximate measurements 2.0×0.67 cm in the sagittal plane and 2.5×1.0 cm in the dorsal plane, with narrowing of the fat adjacent to the spinal cord (mass effect), which was more pronounced at L4. In the contrast phase, there was a slight uptake of peripheral contrast and, although the lesion was less delimited than in the previous tomographic examination, it was possible to identify an increase in its dimensions (2.9×0.65 cm in the sagittal plane and 2.9×1.3 cm in the dorsal plane), which extended from the height of the caudal third of L3 to the caudal portion of L5, without any evidence of osteolysis, but with widening of the vertebral canal (Figure 1B).

During the necropsy, part of the corpse carcass (skeleton, part of the musculature, and spinal cord) was submitted to a *post mortem* radiographic examination of the spine, at Diagnostic Imaging Sector of HOSPMEV-UFBA. The enlargement of the vertebral canal from T10 to S2, was more pronounced with an irregular aspect, between L2 and L7. There was presence of intense osteolysis from L1 to S2 and spi-

nous processes from L5 to L7, and bilateral periosteal proliferation from L3 to L7, with an ankylosing aspect (Figure 2A). After the injection of iodinated contrast into the subarachnoid space of the vertebral canal, with the aid of a urethral probe, it was possible to monitor the T13 contrast column up to the level of L1 and caudally at this point there was an interruption of the contrast column, which indicated the absence of flow liquid to L1.

Necropsy revealed intense ankylosis between the lumbar vertebrae (L3 to L7) associated with an increase in local volume and focal area of dorsal depression in S1 topography. Inside the vertebral canal, an intradural-extramedullary firm mass (9.5 × 2.6 × 2.3 cm) was found in the region of lumbar swelling (9.5 × 2.6 × 2.3 cm), which extended from L2 to L6 as irregular and multinodular with protruding areas beyond the pia mater, with yellowish white color (Figure 2B and 2C). Upon sectioning, the tumor mass was compact, regular, and yellowish-white with brownish multifocal areas. There were no gross metastases in any organ or tissue. After necropsy, multiple tissue sections from the mass and other organs were immersed in 10% buffered formalin, routinely processed by the paraffin embedding technique, sectioned into 4 μm sections, and stained with hematoxylin and eosin (HE)[2] and Masson's trichrome[2].

Histologically, there was neoplastic proliferation consisting of moderately pleomorphic cells, which varied between spindle, ovoid, and polygonal, arranged in streaming bundles, occasionally intertwined with cells aligned in palisade in a conjunctive stroma and, sometimes, in a solid mantle supported by loose stroma (Figure 3A). The cytoplasm was undefined, with fusiform to ovoid nuclei, medium to large, sometimes hyperchromatic, slightly granular chromatin, and inconspicuous nucleoli (Figure 3A detail). The mitotic index was high, with an average of 10 to 12 mitoses per 40x field. There was an intratumoral multifocal lymphoblastic inflammatory infiltrate, along with extensive areas of liquefative necrosis, focal axonal demyelination of the adjacent white matter, congestion, multifocal hemorrhage, and diffuse edema (Figure 3B). Neoplastic emboli were not observed in the vascular structures. Masson trichrome staining highlighted moderate capsule and intense diffuse conjunctive stroma (Figure 3C). There was no histologic evidence of metastasis in the examined tissues or changes that need to note.

Microscopic findings indicated the presence of mesenchymal neoplasia, suggestive of a malignant peripheral nerve sheath tumor or fibroblastic meningioma. For confirmation, an immunohistochemical panel[3] was performed with markers in appropriate dilutions: primary antibody anti-factor VIII, glial fibrillary acidic protein (GFAP), vimentin, α-actin for smooth muscle, cytokeratin, protein S-100, specific neuron enolase (SNE), neurofilament, and desmin. The processed sections were embedded in paraffin blocks laminated to 4 μm of the neoplastic tissue, using streptovidin-biotin-peroxidase[4] methods and, for immunomarking diaminobenzidine (DAB), the sections were counterstained with Harris hematoxylin. There was strong and diffuse intracytoplasmic positivity for vimentin (Figure 3D) and S-100 (Figure 3E) and partial for SNE (Figure 3F). For other antibodies, there was no reactivity.

DISCUSSION

The diagnosis of malignant peripheral nerve sheath tumor was established based on history, imaging exams, gross anatomic changes, histologic findings, and was confirmed by immunohistochemistry.

Peripheral nerve myelin sheath tumor (PNMST) may originate from Schwann cells, responsible for the formation of the myelin sheath, or from fibroblasts that make up the endoneurium and epineurium, or both cell types [4]. In view of the varied histopathological aspects of the neoplasia, there are controversies regarding the denomination of the tumor. Therefore, the World Health Organization (WHO) opted for the generic and grouped classification as benign peripheral nerve sheath tumor (schwannoma and neurofibroma) or malignant (malignant schwannoma and neurofibrosarcoma) [4]. However, for definitive diagnosis, immunohistochemical marker assay should be performed and should be correlated with histopathological findings.

PNMST mainly affects dogs from 5 to 12 years old, with an average age of 8 years [4,11,22]. The long interval between the appearance of clinical signs and the definitive diagnosis of neoplasm of the spinal cord is highlighted, due to the difficulty of access to perform computed tomography [7,18,20] and magnetic resonance imaging [7,18]. The present report differs from the cases already described, which presumptive diagnosis was made when the animal was 2 years of age, with the aid of CT and correlation with clinical signs.
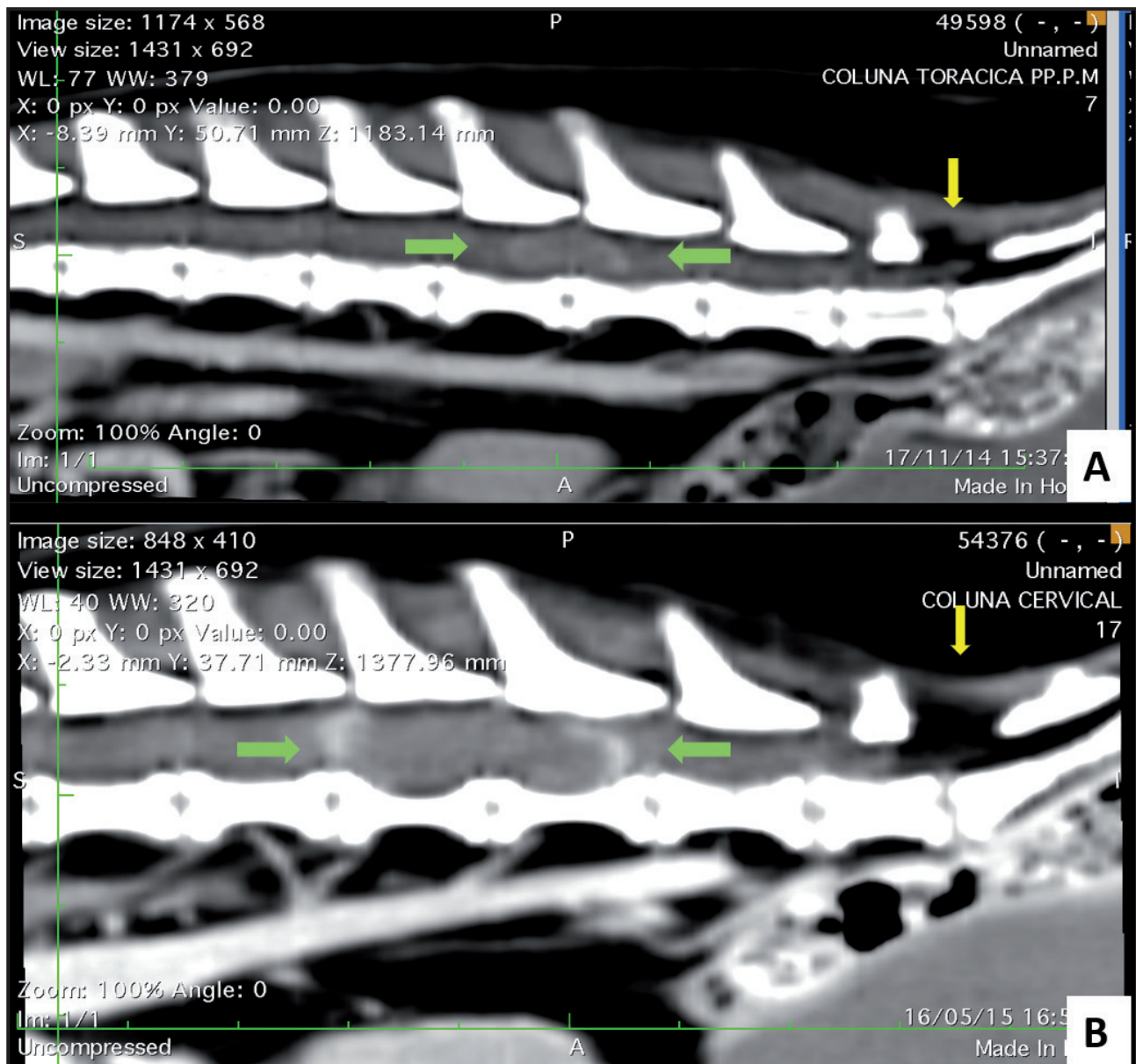
Figure 1. Computed tomography images in sagittal reconstruction, after injection of intravenous contrast, of the lumbar region of a female dog with malignant tumor of the lumbar peripheral nerve sheath, (A) at 2 years of age and in (B) after 2 and a half years. A- 1.35 x 0.42 cm intramedullary hypertenuating area (between green arrows) with slight uptake of peripheral contrast and spina bifida region (yellow arrow) is seen. B- There is an increase in the hyperattenuating area 2.0 x 0.67 cm (between green arrows), with uptake of peripheral contrast and the widening of the vertebral canal adjacent to the spinal cord injury. Yellow arrow indicates the spina bifida region.

In this report, CT was suggestive of intramedullary neoplasia (L3 to L7) and helped compare and monitor the evolution of the process in 6 months, indicating tumor growth. In addition, spina bifida (incidental finding), which had been previously identified by radiographic examination, was also confirmed. Conventional radiography is usually the first imaging examination of choice to assist in diagnosis when changes in the spine are suspected [3], but in this report, it did not allow the identification of the neoplasm, due to limitations caused by the overlapping of anatomical structures and similar radiopacity [3,7]. However, imaging tests that do not cause overlapping of structures such as CT and magnetic resonance are the most commonly indicated because they allow the visualization of small structures and, through the use of contrast, evaluate the vascularization of tissues [3,7,20].

Post mortem radiographic examination revealed intense osteolysis and widening of the vertebral canal (T10 to S2) with ankylosis (L3 to L7), which was confirmed during necropsy. Such observations were justified by the growth of the tumor, which caused compression of the dorsal arches and destruction of the spinous processes of the vertebrae. Ankylosis, in turn, probably
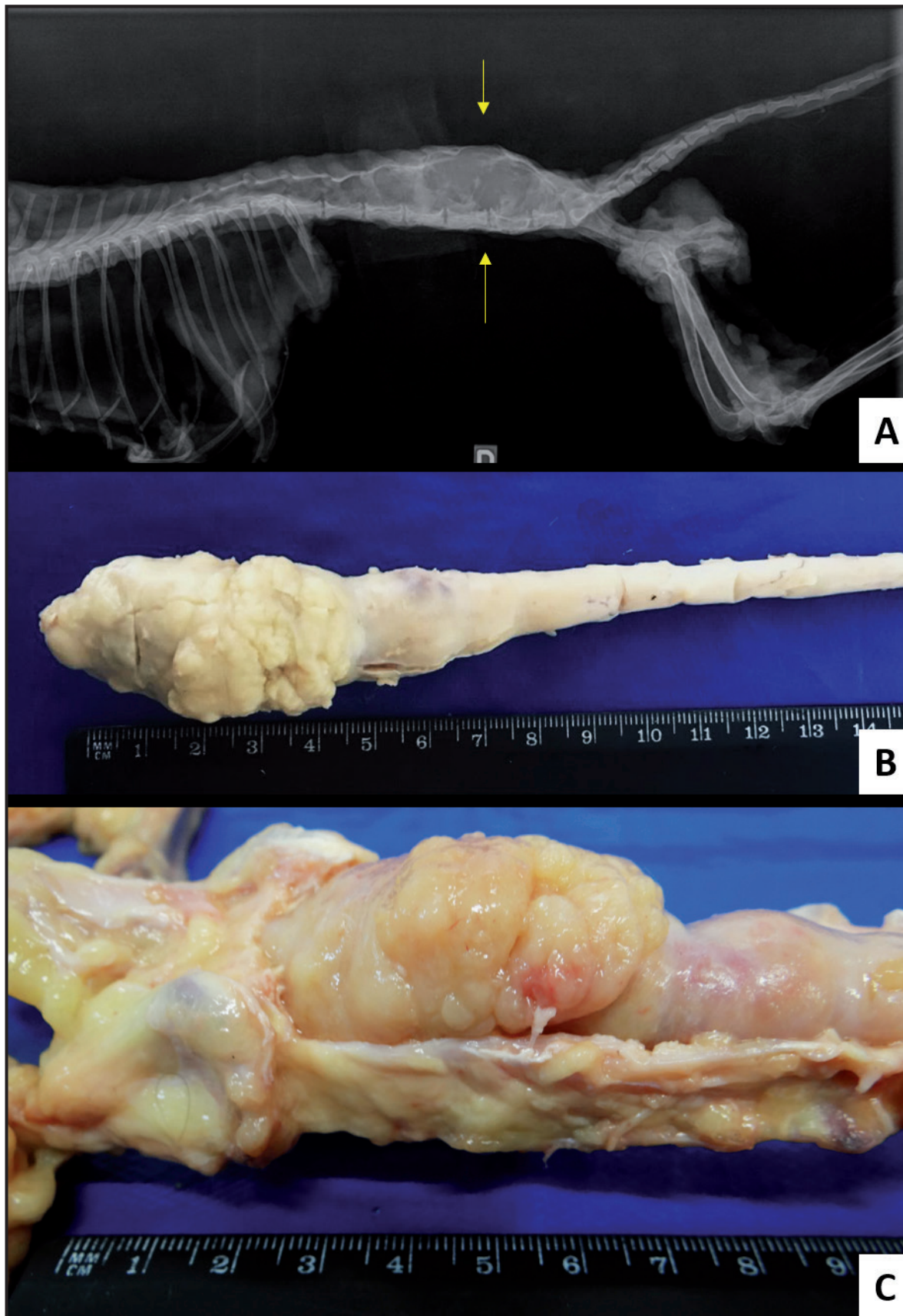
Figure 2. A- Post mortem radiographic image of part of the carcass with enlargement of the vertebral canal (T10 to S2), intense osteolysis of the dorsal arches (L1 to S2) and spinous processes (L5 to L7). B- Partial image of the spinal cord fixed in 10% formaldehyde with enlarged, multinodular and white intradural-extramedullary mass. C- Intradural-extramedullary firm mass in the region of lumbar swelling, extending from L2 to L6 as irregular and multinodular with protruding areas beyond the pia mater, with yellowish white color.
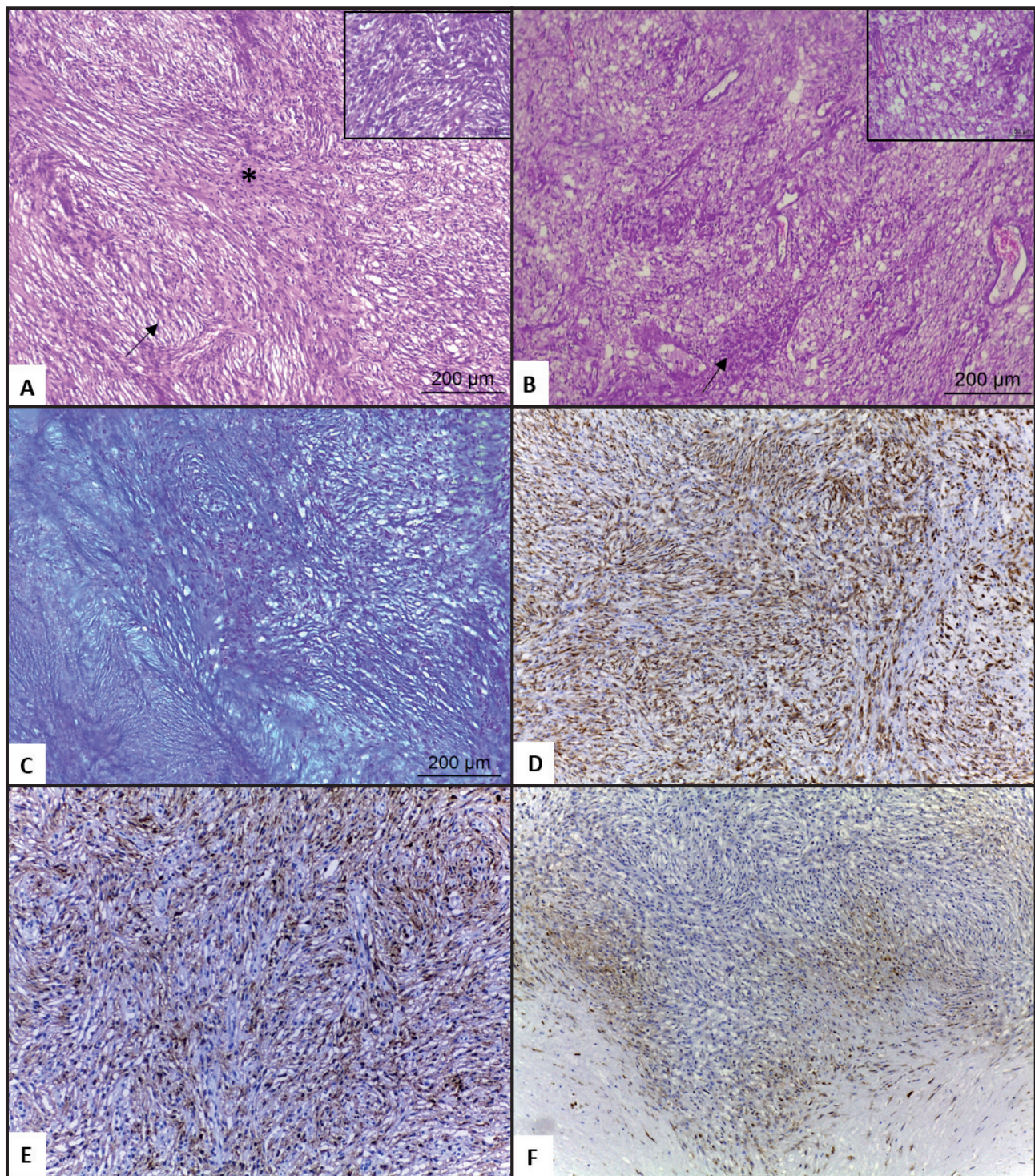
Figure 3. Photomicrograph of a malignant peripheral nerve sheath tumor in a dog. A- Arrangement of neoplastic cells in interlaced bundles or palisade (arrow) and, sometimes, solid mantle supported by loose stroma (asterisk) [HE; 20x]. In detail: intense pleomorphism, fusiform to ovoid nuclei, medium to large, sometimes hyperchromatic, slightly granular chromatin, and inconspicuous nucleoli [HE; 40x]. B- Lumbar spinal cord with axonal demyelination of the focal white substance (detail), multifocal lymphoplasmocytic inflammatory infiltrate (arrow) [HE; 20x]. C- Intense diffuse connective tissue surrounding tumor cells [Masson's Trichrome; 20x]. D- Intense and diffuse labeling for anti-Vimentin antibody [IHC; 20x bar]. E- Intense and diffuse labeling for the anti-S-100 antibody [IHC; 20x bar]. F- Partially positive label for specific neuron enolase antibody [IHC; 4x bar].

resulted from persistent injury, chronic inflammation, and replacement of the articular surface with bone tissue, a similar finding has already been reported [5].

The macroscopic findings were similar to those described by other authors [5,11,13,14,19,21,26]. On necropsy, it was possible to confirm that the mass affected the region of lumbar intumescence and intradural-extramedullary location, different from that observed in CT examinations that pointed to an intramedullary neoplasia. In a comparative study of imaging tests for

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spinal neoplasms, it was demonstrated that CT does not allow an effective distinction between intradural extramedullary and intramedullary tumors [4].

On histopathology, the intense pleomorphism, necrosis, hemorrhage, and high mitotic index were compatible with those described by other authors [4,12,13,19]. Although rare, metastases in dogs have already been observed in lymph nodes, lungs, spleen, liver, and kidneys [10,11,23,25] and, more recently, in the central nervous system and other regions of the spinal cord [19]. In this report, no foci of metastasis were observed. The infiltration of the medulla with focal demyelination of the white matter and axonal degeneration in this case probably occurred due to hypoxia due to tumor growth, which may have generated a decrease in potassium influx and blood supply [1]. This secondary demyelination has also been reported by other authors [2,14,17, 22]. Masson's trichrome staining allowed the identification of the intense fibrous connective tissue, which can be explained by the cellular components of the neoplasm, composed of fibroblasts and perineural cells and, to a lesser extent, Schwann cells [2,25]. Immunohistochemical staining (IHC) was positive for vimentin (mesenchymal origin) and S-100 (neuroglial, ependymal, melanocytic, and Schwann cells) in a strong and diffuse manner. The S-100 and GFAP markings may be absent or vary from weak to strong and multifocal to diffuse [3,11]. Although some authors associate the negative S-100 marking with the malignant tumor variant [11,21], it is known that the differentiation of benign and malignant peripheral nerve sheath tumors should not be limited to the use of S-100, but to a set of other markers [25], similar to those used in this report. For the SNE, the staining was partially positive, which explains the neural and neuroectodermal origin, according to results already described [19]. Thus, based on these findings, a definitive diagnosis of MPNST was established.

The MPNST has no breed predisposition, but it has been reported commonly in large breeds such as Rottweiler, German Shepherd, and Labrador [4,10,13,14,22], and are uncommon in Toy breed dogs [5,19]. The animal in this report was Poodle breed (small), which favored better care and handling, in addition to the increase in appropriate handling to promote more comfort and well-being of the animal for the duration that the animal lived with the paralysis of the pelvic limbs.

Although there is no predisposition for MPNST occurrence in relation to sex, there is consensus regarding a higher frequency in females [2,9], as in this report. In women, it is speculated that there exists a correlation of neoplasia with the hormone progesterone in the development of neurofibromas during puberty and neurofibromatosis during pregnancy [8]. However, in female dogs, hormonal involvement in PNMST occurrence has not yet been proven [9].

The peripheral nervous structures most affected by myelin sheath tumors are the roots of the fifth pair of cranial nerves, which include the brachial (C6-T1) and lumbosacral (L5-S1) plexuses [26]. However, neoplasms can appear in any region of the peripheral nervous system, and the clinical signs vary according to the affected region [20,24]. In this report, the neoplasm involved the region (L3 to L7) and the first clinical sign observed was neurogenic claudication, which is nonspecific and must be differentiated from other orthopedic [11] and neurological diseases. There was paresis of the pelvic limbs, muscular atrophy, and neurogenic bladder resulting from lumbosacral spinal compression and the nerves responsible for nerve stimulation in the pelvic limbs, bladder, and colon [26].

The appearance of MPNST in the spinal canal represents an unfavorable prognosis [11], since there is no curative treatment, only palliative, through spinal decompression surgeries [5, 15]. In this report, the presumptive diagnosis obtained by CT resulted in the choice of conservative treatment, which contributed to the stability of the clinical picture for four years. Surgical procedures were not considered due to the size of the tumor and location of risk, since manipulation could lead to greater neurological impairment, including increased pain and worsening of motor manifestations [6,13,18]. There are reports of a palliative surgical procedure for intramedullary tumors [12] and MPNST [14], but without success, resulting in euthanasia. Radiotherapy, in these cases, is a more viable therapeutic option [6], but it was not used in this case because of being unavailable in the city where the animal lived.

To the best of our knowledge, MPNST should be included in the differential diagnosis of spinal disorders, even in uncommon cases of small and young breeds. For suspicion of such diseases, imaging tests, mainly CT and magnetic resonance imaging, assists in the presumptive diagnosis and monitoring of the case. In the present case, histopathology suggested a

diagnosis of MPNST or fibroblastic meningioma due to similar cellular characteristics and, thus, the importance of performing an immunohistochemical panel to confirm the diagnosis is reiterated.

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