



CASE REPORT

Undifferentiated Carcinoma of Unknown Origin in the Lumbar Spine of a Dog

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ABSTRACT

An 11-year-old Yorkshire Terrier dog presented with progressive ataxia and paraparesis of 1 month duration. The abnormality was localized to the T13-L2 segment by neurologic examination and CT. MRI showed a space-occupying lesion compressing the spinal cord and adjacent osteolysis of the L1 vertebra. A diagnosis of poorly differentiated carcinoma with high malignancy was reached by histopathology of the biopsy samples. Metronomic chemotherapy was applied, but the patient was euthanized at 133 days after first presentation. Samples of the lumbar mass, pulmonary nodules, and lymph nodes were obtained during necropsy and evaluated with histopathology and immunohistochemistry (IHC). Undifferentiated carcinoma suspicious of transitional cell carcinoma was confirmed, but the exact origin of the tumor was undetermined. This is the first case report of an extradural primary carcinoma of unknown primary in the canine spinal cord and paravertebral region.

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INTRODUCTION

Spinal cord tumors can be subdivided into extradural, intradural-extramedullary and intramedullary locations and occur in dogs of any age. The extradural form comprises approximately one half of all spinal cord tumors and includes primary bone tumors such as osteosarcoma, fibrosarcoma, chondrosarcoma, hemangiosarcoma (Levy *et al.*, 1997). It may be metastases to vertebral bone and surrounding soft tissue, requiring further evaluation for the primary, and carcinomas are one of the most common types. Paresis/paralysis, dysuria/dyschezia, pain, hyperesthesia and other miscellaneous signs are associated with spinal cord compression by space-occupying lesions in the vertebral canal or paravertebral region and never pathognomonic and vary according to the specific segment affected. The severity of these signs depends on the degree of (1) compression, destruction, edema and hemorrhage of the neurologic tissue, and (2) the compensation (Bagley, 2010).

Surgery is performed to obtain samples for histopathology, to resect the tumor if possible and to decompress the spinal cord, but rarely is excision complete. Therefore, ancillary therapies, chemotherapy or radiotherapy should be performed. Presurgical evaluation of the location and extent of neoplastic involvement can be made by CT/MRI or myelography (Luttgen, 1992). Cerebrospinal fluid (CSF) is often cytologically normal. Histopathology yields a definitive diagnosis and assists in treatment planning (Bagley, 2010; Chung *et al.*, 2014).

History and clinical evaluation: An 11-year-old intact female Yorkshire terrier presented with ataxia, urine leakage, dyschezia, restlessness, and sporadic pain. From mild staggering gait, clinical signs progressed gradually over 1 month and reached hindlimb astasia in recent 7 days despite trials of NSAIDs, steroids and acupuncture. She showed kyphosis, paraparesis with absent postural reactions and mildly exaggerated spinal reflexes, normesthesia. The lesion was localized to the T13-L2 segment.

Diagnostics included CBC, serum-chemistry, urinalysis, radiography of the thorax, abdomen, spine and abdominal ultrasonography. The results revealed leukocytosis (52 m/mm^3) left-sided osteolysis of the L1 vertebral pedicle and body with indistinct margins (Fig. 1). An amorphous mass measuring 1.5 cm in height with homogenous hypo-echogenicity and mild vascularization was identified around the vertebra within the retroperitoneal space by ultrasonography.

A full-body CT scans and thoracolumbar MRI was performed (Fig. 2). An irregularly shaped soft tissue density mass with a mild rim sign that extended inside the vertebral canal was detected at the level of the left vertebral pedicle and body of L1, corresponding to the region of osteolysis. Spinal cord was compressed with relatively smooth margins; the absence of invasion into the dura was not certain, although no parenchymal change was observed. Five pulmonary nodules were identified, which were suspected to be metastases.

Imprint cytology of three 5-mm punch biopsy samples showed clump cells having visible multiple nucleoli and

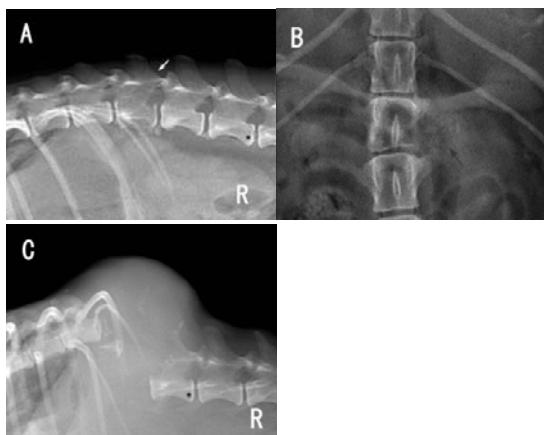


Fig. 1: Thoracolumbar radiographs at first presentation. Decreased opacity of first lumbar vertebral body (A) and soft tissue-opacity mass (B). Before euthanasia (C) The vertebral discontinuity is distinct; L1 and L2 vertebrae are completely unidentifiable, while T13 is nearly obliterated and the cranial part of L3 (*) also exhibits severe osteolysis.

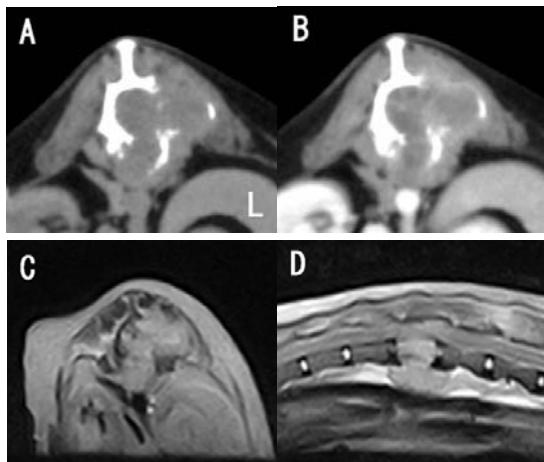


Fig. 2: Pre- and post-contrast CT images (A, B) and T2-weighted MRI images (C, D) showing osteolysis of the L1 vertebral body and pedicle and the massive lesion occupying the ventral of the vertebra. The mass extends to the vertebral canal and compresses the spinal cord.

cytoplasm containing secretory material (Fig. 3). A diagnosis of unidentified metastatic carcinoma with two or more mitotic figures per high power field (HPF) was reported by the pathologist with assessment that this case was not considered to be a primary spinal or vertebral neoplasia. Brain MRI and CSF analysis were conducted but no abnormalities were found.

Treatment: The owner did not consent to surgical debulking or conventional chemotherapy. Palliative care and metronomic chemotherapy were chosen, using cyclophosphamide (12.5 mg/m^2 , SID) and piroxicam (0.3 mg/kg, SID). With episodic complaint of pyrexia and pain, NSAID, tramadol and fentanyl were prescribed and adjusted as needed. However, the patient's condition continued to deteriorate, and she showed flaccid paraplegia with anesthesia, prominent outward growth of the mass.

Humane euthanasia was elected at 19 weeks as severe cachexia, acute ascites and lymphedema of caudal half. The patient's mobility and comfort were severely affected. Vertebral column discontinuity due to complete osteolysis of T13, L1 and L2 was noted on radiographs (Fig. 1-C).

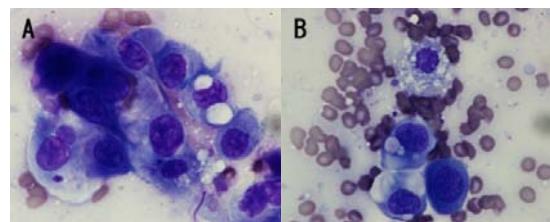


Fig. 3: Cytology of the mass with H&E stain (A, B; $\times 1000$).

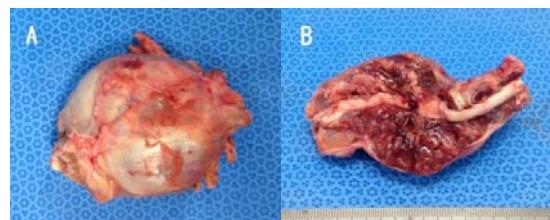


Fig. 4: Gross appearance (A) and cut surface (B) of the mass.

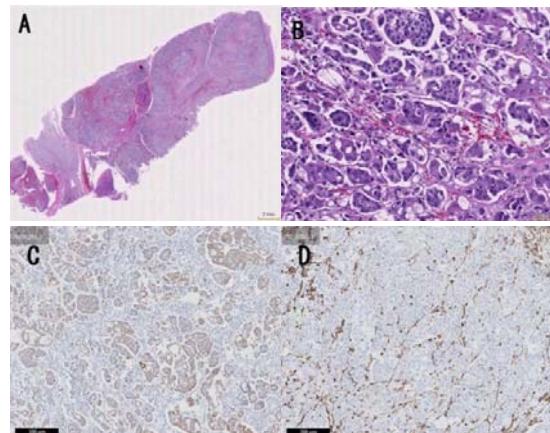


Fig. 5: Histopathologic examinations. (H&E) and immunohistochemistry (C; pan-cytokeratin, D; vimentin)

Necropsy and histopathologic findings: At necropsy, the mass measured $6 \times 5 \times 4 \text{ cm}$ was well-circumscribed by paravertebral muscle fascia (Fig. 4-A) and occupied from T12 to L4 segments and held the separated bony columns to one another. The cut surface appeared coarse, mottled dark-red (Fig. 4-B). Spinal cord maintained its continuity with corrugated running and mild bulging at the level of osteolysis. Tissues of spinal cord, muscle fibers and neoplastic lesion were entwined and adhered. Numerous nodules in the lung lobes but no neoplastic findings in any other organs were observed. Samples were obtained from the paravertebral/spinal lesion, pulmonary nodules and tracheobronchial, lumbar and medial iliac lymph nodes.

Histopathologic examination (IDEXX laboratories, USA) confirmed the presence of epithelial neoplastic cells that reported as moderately pleomorphic, forming confluent nests or cords and exhibiting a scant to moderate amphophilic cytoplasm and variably sized oval, rounded or slightly angular nuclei, with multiple prominent nucleoli (Fig. 5A & 5B). Neural tissue, possibly spinal cord, was evident at the edge of the specimen. The mitotic index was 6 per HPF. The neoplastic cells in the lung nodules and lymph nodes exhibited similar characteristics. Immunohisto-pathologic stain of the mass showed strong immuno-reactivity with pan-cytokeratin while negative

with vimentin (Fig. 5C & 5D). Based on these findings, the diagnosis was made as a poorly differentiated, unidentified, extradural spinal cord carcinoma with metastases to the lung and lymph nodes.

DISCUSSION

Metastatic carcinoma of unknown primary (MCUP) refers to a biopsy-proven metastatic neoplasia in the absence of an identifiable primary despite complete diagnostic work-up (Rossi *et al.*, 2013). MCUP is the seventh most frequently occurring tumor with an incidence of 0.5-10% of all newly diagnosed (Scheidhauer *et al.*, 2000) and the fourth most common cause of cancer-related death in human medicine (Rossi *et al.*, 2013). The nature of MCUP includes early dissemination, an unpredictable pattern of metastasis and aggressive biological behavior accompanying a dismal prognosis with a median survival time of 6-12 months (Batistatou *et al.*, 2013).

Some possible explanations for the development of MCUP have been suggested, such as 1) the primary tumor may remain too small for clinical detection, 2) spontaneous immune-mediated regression of the primary tumor, or 3) dormancy after seeding the metastasis (Rossi *et al.*, 2013). Systemic metastasis may become apparent before the clinical detection of the primary tumor, or the clinical signs associated with the metastasis may not be typical of the primary tumor (Scheidhauer *et al.*, 2000).

Due to a lack of guidelines for diagnosis and treatment, MCUP prognosis is poor irrespective of the anatomical origin. Therefore, histological subtype of the neoplasia is important, although treatment is empirical and response is not satisfactory (Rossi *et al.*, 2013). Metronomic chemotherapy in this case could not suppress the progression, and it took only four months for three consecutive vertebrae to be lysed completely.

Regarding previous reports of MCUP in veterinary medicine, there was one retrospective study of 21 dogs with metastatic tumor of unknown primary. MCUP was the most common diagnosis (57.1%, 12/21; eleven undifferentiated carcinoma, one squamous cell carcinoma) followed by sarcoma, melanoma, and mast cell tumor (Rossi *et al.*, 2013). In those eleven cases of undifferentiated carcinoma, lungs, lymph nodes and spleen were frequent locations and two involved either the paravertebral muscles or vertebral body. Mean survival time (MST) of these 11 dogs was 94 days and that of dogs with or without any treatment was 165 days and 7 days, respectively. A dog treated with surgery, chemotherapy and radiotherapy for a paravertebral muscular lesion had the longest survival time of 504 days. Another dog with multiple pulmonary lesions treated with metronomic chemotherapy survived for 30 days. Other treatment options used in that study included firocoxib and toceranib.

In our case, pathologists reported the diagnosis of MCUP because the exact tumor type was unclear but the lesion was strongly suggestive of a carcinoma with a high grade of malignancy. Nevertheless, there was no previous disease history or evidence of neoplastic changes in other organs including the urinary system, mammary glands and brain despite the complete diagnostic work-up and an additional CT scan before euthanasia. According to the pathologist's experience, the overall morphology shown by

IHC supports a metastatic TCC, but there are no epithelial stains that may precisely confirm the origin of this undifferentiated neoplasia. This uncertainty is mirrored in human medicine, where the primary site cannot be identified even at necropsy in approximately 70% of patients (Rossi *et al.*, 2013).

There are a few reports of a primary neoplasm of an unexpected cell type in the canine paravertebral or spinal region without involvement elsewhere. Two spinal mast cell tumors (Moore *et al.*, 2002; Guevar *et al.*, 2013), seven vertebral myxoma/myxosarcomas (Khachatrian *et al.*, 2009) and one spinal glioblastoma multiforme were reported (Röthlisberger *et al.*, 2012).

To the authors' knowledge, undifferentiated carcinoma or primary TCC associated with the canine spinal cord and vertebral column have not been reported. As a primary carcinoma is not typical in this region, it was difficult to achieve a definitive diagnosis due to the expense of additional testing and the time required in the context of a poor prognosis of metastatic neoplasia. Limitation in this case is the lack of histopathology of other organs but the organs appeared to be grossly normal at necropsy, and advanced imaging prior to euthanasia did not suggest any abnormalities. Conclusively, this is a case of a highly aggressive metastatic carcinoma of unknown primary that is strongly suspected to TCC invading the spinal cord and vertebral column. This case report describes a solitary, undifferentiated, primary extradural carcinoma in the canine spinal cord and paravertebral region with recognized metastases to the lungs and the thoracic and abdominal lymph nodes with highly aggressive biological behavior.

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