Paramedullary plasmacytoma originating from the first cervical vertebra (C1) in an 8-month-old warmblood weanling with tetraparesis: Clinical and pathological findings

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October 14, 2022

Abstract

To the authors' knowledge there is only one report in the literature, dealing with paramedullary plasmacytomas in horses as so-called "break out lesions", originating from the bone marrow of a vertebra and invading the epidural space (Drew and Greatorex 1974). Our case report describes the clinical and patho-morphological findings of such a case. The affected 8-month-old warmblood weanling colt exhibited acute tetraparesis thus, a spinal cord lesion in the cervical column was suspected. Computed tomography revealed osteolytic lesions in C1 and a heterogeneous mass within the respective segment of the vertebral canal. By means of patho-morphological examination, with the aid of transmission electron microscopy, a plasmacytoma was identified, that had grown out of the bone marrow of C1 into the epidural space, locally compressing the spinal cord. In tetraparetic, young horses traumatic spine cord injuries, cervical vertebral malformations and infectious diseases of the central nervous system represent common differentials. However bone-dissolving tumours such as paramedullary plasmacytomas should be considered as a further possible cause in the presence of severe neurological deficits.

Title

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Summary

To the authors' knowledge there is only one report in the literature, dealing with paramedullary plasmacytomas in horses as so-called "break out lesions", originating from the bone marrow of a vertebra and invading the epidural space. Our case report describes the clinical and patho-morphological findings of such a case. The affected 8-month-old warmblood weanling colt exhibited acute tetraparesis thus, a spinal cord lesion in the cervical column was suspected. Computed tomography revealed osteolytic lesions in C1 and

a heterogeneous mass within the respective segment of the vertebral canal. By means of pathomorphological examination, including transmission electron microscopy, a plasmacytoma was identified, that had grown out of the bone marrow of C1 into the epidural space, locally compressing the spinal cord. In tetraparetic, young horses traumatic spine cord injuries, cervical vertebral malformations and infectious diseases of the central nervous system represent common differentials. However bone-dissolving tumours such as paramedullary plasmacytomas should be considered as a further possible cause in the presence of severe neurological deficits.

Keywords: horse; tetraparesis; vertebra; spinal cord; tumour

Introduction

In horses spinal cord dysfunction can have several causes, including traumatic injury, cervical vertebral stenotic myelopathy or malformation and infectious diseases such as protozoal or viral myeloencephalitis (MacMillan *et al.* 2021). Neoplastic disease is considered a further differential, however, especially in young horses, tumours originating from the cervical vertebrae represent a rare event. To date, there is only one report in the literature of a plasmacytoma with invasion of the vertebral canal (Drew and Greatorex 1974). The aim of this case report was to describe clinical, imaging and pathological features of a paramedullary plasmacytoma in a young horse, in distinction to other variants of this neoplastic disease.

Case history

An 8-month-old warmblood weanling colt was presented to the Department for Horses of the University of Leipzig for acute non-ambulatory tetraparesis. Four days before presentation, the foal was found in the stable with neck asymmetry, which was deviated mildly to the right. The colt was standing but unable to extend the neck and to grab the hay from the ground. On the right cranial side of the neck, a swelling was noticed by the owner. A trauma was suspected. The foal was treated for two days by the referring veterinarian with antibiotic (Cefquinom, 1 mg/kg body weight (BW) q. 24h) and non-steroidal anti-inflammatory drugs (Flunixin meglumine, 1.1mg/kg BW q. 24h). On the morning of referral to the Department for Horses of the University of Leipzig the foal was found lying down in the stable and was unable to rise.

Clinical findings

On presentation the foal was bright, alert and responsive, but in lateral recumbency and unable to stand. The colt was classified with grade 5/5 ataxia based on a modified grading system for cervical spinal cord disorders (Mayhew *et al.* 1978; DeLahunta and Glass 2009). The foal presented with a body temperature of 37.8°C, a heart rate of 52 beats/min and a respiratory rate of 22 breaths/min. He was able to eat and drink food and water within his reach. He made several unsuccessful attempts to rise but settled quickly and did not require sedation.

His neck appeared to deviate mildly to the right in the proximal neck region, and there was a diffuse swelling at the level of the third to fifth cervical vertebra (C3–C5). The swelling showed increased warmth and was painful to palpation. Increased muscle tone of the neck was present and the cervicofacial reflex of the left cervical side was decreased. The foal showed volitional movement of the forelimbs and weaker volitional movement of the hindlimbs. Examination of spinal reflexes revealed slight hyperreflexia of both patellar reflexes and slightly decreased tail tone. The foal was continent and had been passing both urine and faeces. His response to pain stimulus was inconsistent in both hindlimbs when the skin was tapped with a needle. Clinical findings suggested a focal spinal cord lesion located between C1 and C5.

Haematological and biochemical blood analysis included the following findings: mild increase in erythrocytes (10.66 T/l, reference interval 7.4–10.2 T/l), mild increase in segmented neutrophils (70%, reference interval 30.4%–65.4%), mild hypocalcaemia (2.68 mmol/l, reference interval 2.72–3.15 mmol/l), mild hypophosphatemia (1.08 mmol/l, reference interval 1.40–2.16 mmol/l), severe sideropenia (3.2 µmol/l, reference interval 20.66–47.67 µmol/l), mild increase in fibrinogen (4.4 mmol/l, reference interval 2–4 mmol/l), mild hypoalbuminemia (22.9 mmol/l, 24.8–32.7 mmol/l), mild hypocreatinemia (64 mmol/l, reference interval 80.7–125.7 mmol/l), mild increase in creatin kinase (457 mmol/l, reference interval 151–374 mmol/l).

In an attempt to reduce inflammation and improve clinical symptoms, the colt was administered flunixin meglumine intravenously (1.1 mg/kg BW). Medication did not improve the clinical symptoms and the owner agreed to further diagnostic tests. A computed tomography (CT) examination of the head and cranial cervical spine was performed.

Computed tomography examination and findings

The CT examination was done at the Department for Horses of the University of Leipzig, using a multi-detector row CT unit (Mx8000 IDT 16 CT scanner, Philips Medical-Systems DMC GmbH, Hamburg, Germany). The colt was sedated with Romifidine (0.08 mg/kg IV) and Butorphanol (0.08 mg/kg IV) and general anaesthesia was induced with Ketamin (2.2 mg/kg IV) and Diazepam (0.08 mg/kg IV). Anaesthesia was maintained with an intravenous continuous rate infusion (CRI) of triple drip (Guaifenesin 100 mg/ml; Romifidine 0.1 mg/ml, Ketamine 2.2 mg/ml) at a rate of 2.2 ml/kg/h (Davidson 2008). The colt was placed in ventral recumbency with the head and neck in an extended position. For image acquisition the following settings were used: tube voltage 120 kV, tube current 234 mAs, rotation time 0.75 s, pitch 0.438 and 1 mm slice thickness with a spacing between the slices of -0.5. The window width was set at 2000 HU (Hounsfield units) and the window level at 500 HU with a 512 × 512 matrix.

The CT scan (Figure 1) showed changes consistent with osteolysis of both cortical and cancellous bone of the right condyle of the occiput as well as the left side of the vertebral body of C1 (Figure 1A), including the left part of the arcus dorsalis (Figure 1B). Moreover, thickening of the cortical plate and new bone formation was observed at the proximal aspect of the left ala atlantis (Figure 1C). The transverse plane images also revealed the presence of a heterogeneous mass in the vertebral canal, causing right dorsal deviation of the spinal cord (Figure 1B–1C). The mass showed a radio density of approximately 33–44 HU, hereby showing lower CT numbers measured for surrounding muscle tissue (HU 52–61). The permeative character of the described bone lesions, led to the diagnosis of a pathologic fracture due to osteomyelitis or neoplasia. The presence of a tumour, an abscess or rather a hematoma were considered plausible differentials for the mass located within the cervical canal. Because of the poor prognosis, the colt was humanly euthanized.

Pathological examination and findings

During necropsy, the gross examination revealed an approximately 3.5 × 2.5 × 0.7 cm, wine-red to beige coloured, tightly elastic, intraspinal epidural neoplasm, located dorsolaterally with orientation to the left on the dura mater at the level of C1 (Figure 2A). Locally, the spinal cord showed mild, acute, multifocal to confluent, subdural hemorrhage. After maceration of C1, moderate to severe, multifocal to confluent osteolysis with destruction of the regional bone in the left dorsal arch, partly in the transition to the left ventral arch and the left cranial articular fovea was determined (Figure 2B).

Histologically, the neoplasm was unencapsulated, infiltrative and moderately cell rich. It consisted of predominantly loosely packed round cells within moderate amounts of a pre-existing fibrovascular stroma (Figure 2C). The neoplastic cells were round to oval, average 15 µm in diameter, had distinct cell boundaries and predominantly small amounts of an amphophilic, homogeneous cytoplasm. The round to oval cell nuclei were eccentrical and had finely stippled, hypochromatic chromatin and up to two distinct nucleoli. Within the tumour cell population, there was moderate anisocytosis and anisokaryosis, the ratio of nucleus to cytoplasm was shifted to the nucleus, and there were individual giant cells containing up to four random arranged nuclei. The mitotic rate was up to six, sometimes bizarre, mitoses per 2.37 mm^2. Small proportions of the neoplastic cells were infiltrating the surrounding area. There were areas of hemorrhage and hemosiderin-containing macrophages and also a mild, acute, multifocal, purulent inflammation. By methyl green pyronine stain single cells showed low to moderate amounts of intracytoplasmic ribonucleic acids.

With the immunohistochemical markers CD3 (T lymphocytes; A0452, Agilent Technologies, Santa Clara, USA), CD79a (B lymphocytes; clone HM57, MCA2538H, Bio-Rad Laboratories, Inc., Hercules, USA), CD 20 (B lymphocytes; PA5-16701, Thermo Fisher Scientific, Waltham, USA), MUM-1 (plasma cellular multiple myeloma oncogene 1; clone MUMp1, M7259, Agilent Technologies, Santa Clara, USA), kappa light chain (κ side chain of immunoglobulins; A0191, Agilent Technologies, Santa Clara, USA) and lambda light chain

(λ side chain of immunoglobulins; clone BIg501E, BIG501E, VMRD, Inc., Pullman, USA), the neoplastic tumour cell population was predominantly indistinct to immuno-negative (not shown).

By means of a transmission electron microscopic examination (TEM), the tumour cells showed a plasma cell morphology at the ultrastructural level. Pleomorphic, large cells with an eccentrical nucleus and sometimes moderate amount of cytoplasm were determined (Figure 2D). Most of the nuclei were large and irregular in shape, some of them contained prominent nucleoli. In addition, the tumour cells contained abundant amount of rough endoplasmic reticulum (Figure 2D). Often, dilated cisternae of rough endoplasmic reticulum were detected, so that the tumour cells as a whole had a vacuolated appearance (Figure 2D). The dilated cisternae of the endoplasmic reticulum showed a flocculent material, which can be assumed to be consistent with globulin precipitates, a feature of antibody-producing plasma cells.

Discussion

Various terms for malignant neoplastic processes, originating from plasma cells exist in the literature. It is a heterogeneous tumour disease group with many variants. Only few descriptions are available, especially for young horses.

Most of the knowledge of this special tumour entity derives from human medicine, but it is unclear to what extent the classification and diagnostic criteria for human plasma cell tumours are applicable to the horse (Edwards *et al.* 1993).

Basically, the following variants can be distinguished depending on the organs affected: Multiple myeloma is a malignant neoplastic process originating from the plasma cell and is characterized by multifocal to diffuse growth pattern within the bone marrow and destruction of the affected bone (Edwards *et al.* 1993; McConkey *et al.* 2000). However, in addition to this medullary form, extramedullary forms can be distinguished in which the bone marrow is not affected (McConkey*et al.* 2000). In the horse, extramedullary plasmacytomas have been described, for example, in lymph nodes, spleen, lung, liver, kidney, brain, orbit, pituitary gland, adrenal cortex, tongue muscles, as well as in nervous and connective tissue (Markel and Dorr 1986; Edwards *et al.* 1993; McConkey *et al.* 2000).

Some authors also distinguish tumours characterized by a single lytic bone lesion and call these "solitary plasmacytoma of bone" (Frassica*et al.* 1989; Edwards *et al.* 1993). However, there is controversy as to whether this is just an early form of multiple myeloma or whether it represents a distinct variant of the disease (Frassica*et al.* 1989).

Further variants derived from human medicine exist such as "smoldering (asymptomatic) multiple myeloma", which is an asymptomatic plasma cell proliferation disorder associated with a high risk of developing symptomatic multiple myeloma (Kyle *et al.* 2007).

When single or multiple osteosclerotic bone lesions are present, it is also referred to as "osteosclerotic myeloma" (Kyle and Greipp 1988).

In addition, leukemic forms of the disease are rarely described (Edwards*et al.* 1993). Plasma cell leukemia is present when the number of neoplastic plasma cells in the blood is ¿2,000/µL and when they account for at least 20% of the differential blood count (Bernasconi *et al.* 1989; Edwards *et al.* 1993).

Furthermore, in humans a distinction between secretory and non-secretory tumour forms exists, whereby in the secretory form monoclonal antibodies are produced by the tumour cells and paraproteins are detectable in serum or urine (Kyle and Greipp 1988; Edwards *et al.* 1993; McConkey *et al.* 2000).

Regarding the typical punched-out lytic bone lesions of the C1, the intraspinal tumour mass and the pathomorphologic findings, especially considering the ultrastructure of the tumour cells, the presence of a malignant neoplasm originating from plasma cells is diagnosed. The immunohistochemical examination in the present case was inconclusive. A probable reason for this could be the different stages of differentiation of the tumour cells.

Only based on the CT findings (lytic bone lesions) and the cell morphology, a "nonproductive osteoblastic osteosarcoma" should be considered primarily for differential diagnosis. However, due to the lack of evidence of osteoid, which should be found in small amounts even in a "nonproductive osteoblastic osteosarcoma" (Thompson and Dittmer 2017b), as well as the rather atypical localization for the horse (Bush*et al.* 2007; Thompson and Dittmer 2017b), this seems unlikely. In particular, the tumour cell invasion into the vertebral canal (Thompson and Dittmer 2017a) as well as the morphology typical for plasma cells on an ultrastructural level such as an eccentric nucleus, much cytoplasm with abundant rough endoplasmic reticulum with partially dilated cisternae (Curtis *et al.* 1975) suggest a plasma cell tumour as cell of origin.

The peculiarity of this case report is the age of the affected horse (8 months old), the localization (C1) and the associated clinical symptoms (tetraparesis) as well as the manifestation of the disease (paramedullary plasmacytoma). To the authors' knowledge, the term "paramedullary plasmacytoma" used in human medicine (Hameed *et al.* 2020) has received little attention in veterinary medicine to date, although it fits well to characterize the growth of the tumour throughout the compacta of the vertebral body with invasion into the vertebral canal. To date, there is only one other case report in the literature describing the invasion of a plasma cell tumour into the vertebral canal in a horse (Drew and Greatorex 1974). Therefore, in the present case, a solitary localization of the tumour in the C1 is most likely but with residual uncertainty. Maybe the lesions found here can be regarded as the initial stage of multiple myeloma. Whether there are further lytic bone lesions remains unclear, because a full body CT scan was not feasible in the weanling colt. However, based on the blood count and serum chemistry, there were no indications of a systemic disease like a secretory active multiple myeloma.

Conclusions

In veterinary medicine the term "paramedullary plasmacytoma" is also suitable for affected horses to describe a particularly rare form of this tumour disease. Rarely, young animals under one year of age may be affected. Especially in young animals, not only common trauma to the spine should be considered causative for signs of paresis. In terms of a pathological fracture or bone lesion, also neoplasia such as para- or medullary plasmacytomas with concurrent osteolysis, may be an important differential diagnosis. These can be well visualized with advanced imaging methods such as CT and confirmed by consecutive necropsy.

Author' declaration of interests

No conflicts of interest have been declared.

Ethical animal research

No experimental animals were used in this case report.

Source of funding

No funding was provided for this study.

Acknowledgements

The authors thank Lars Riesche for macroscopical preparation.

Authorship

All the authors participated in the article preparation and have approved the final version.

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Figure legends

Fig. 1: Transverse plane computed tomography images (right is to the left) of an 8-month-old warmblood colt with acute onset of non-ambulatory tetraparesis. An artefact caused by damaged detectors is marked with asterisks. A) Focal, well defined osteolytic lesions at the right ventral aspect of the right condylus occipitalis (white arrow) at the level of the atlanto-occipital joint. B–C) Concurrent bone destruction with "moth-eaten" pattern, involving the arcus dorsalis of C1 (white arrow) and periosteal new bone formation at the proximal aspect of the left ala atlantis of C1 (black arrow). Note right dorsal displacement of the spinal cord (white circle) caused by a mass located within the vertebral canal.

Fig. 2: 8-month-old warmblood colt suckling with paramedullary plasmocytoma

originating from the bone marrow of C1 with invasion of the epidural space. A) Intraspinal epidural neoplasm (oval), dorsolaterally left on the spinal cord (black arrow). Segment detached from the vertebral canal at the level of C1. B) Macerated C1 with destruction of the local bone especially in the left dorsal arch (black arrow), partly in the transition to the left ventral arch (white arrow). C) Loosely packed round cells, with moderate anisocytosis and anisokaryosis. Note the eccentric and huge nuclei in relation to the cytoplasm, the binuclear cells (circle), sometimes a "halo" (arrow) and the bizarre mitoses (arrowhead). Haematoxylin

and eosin, scale bar = 50 µm. D) A tumour cell on the ultrastructural level. Note the abundant amount of rough endoplasmic reticulum (arrow) with dilated cisternae (arrowhead) containing flocculent material. TEM Libra 120 (Zeiss, Oberkochen, Germany), 80 keV. Scale bar = 2500 nm.

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