Case Report

Metastatic Tumor in Pregnancy: Placental Germ Cell Tumor with Metastasis to the Foal

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Abstract

Placental neoplasia was observed in an otherwise healthy Quarter Horse mare; subsequently, the mare’s 52-day-old foal was examined because of hindlimb ataxia, urinary incontinence and abnormal raised lesions of the distal limbs. Clinical and biochemical findings were supportive of liver disease and lumbosacral injury. Ultrasonographic evaluation of the abdomen suggested a liver mass which was confirmed with computed tomography (CT) and determined to be neoplastic via histopathologic evaluation of a liver biopsy sample. Regions of lysis affecting both femurs and third metacarpal bones, and a complete oblique sagittal fracture through the body of the first sacral vertebra were present on CT. Supportive care was provided until CT confirmation of diffuse hepatic neoplasia and vertebral fracture. Necropsy revealed a large, multinodular mass within the liver and a pathologic fracture of the first sacral vertebral body. Histopathologic comparison between neoplastic cells examined from the placenta and foal confirmed metastases of a germ cell tumour. Placental tumours are rare in all species; however, when noted in horses, clinicians should be aware of the possibility of metastatic spread to the foal.

ABBREVIATIONS

CBC: Complete Blood Count; HCT: Hematocrit; CK: creatine kinase; AST: Aspartate Amino Transferase; GGT: Gamma Glutamyl Transferase; CSF: Cerebrospinal Fluid; SDH: Sorbitol Dehydrogenase; HU: Hounsfield Unit; CT: Computed Tomography; NSGCT: Nonseminomatous Germ Cell Tumor; GCT: Germ Cell Tumor; CNS: Central Nervous System

INTRODUCTION

Neoplasia in the horse is uncommon, and the finding of neoplasia in a young foal is extremely rare. Similarly, while masses in the placenta of mares are seen with a comparatively higher frequency, they are typically benign in nature. This report describes the history, presentation, diagnostics, and outcome of a nonseminomatous mixed germ cell tumor in a foal that likely metastasized from the placenta.

CASE PRESENTATION

A 4-hour-old 54-kg (118-lb) Quarter Horse filly born to a recipient mare was presented to the Lloyd Veterinary Medical Center for diarrhea since birth. Abnormal clinical findings included tachycardia, dehydration, and diarrhea. Omphalophlebitis was diagnosed based off of gross and Ultrasonographic appearance. After 5 days of supportive care, the filly was discharged as the diarrhea had resolved and the remainder of the physical examination was unremarkable. During hospitalization, routine post-partum examination of the mare’s reproductive tract was unremarkable. However, the placenta was markedly distorted by numerous multifocal, nodular, friable, firm to mineralised, red to yellow masses ranging in size from 1 to 14 cm (Figure 1). The largest focal nodular mass (14 cm) was located at the junction of the umbilical vasculature to the placenta, surrounded by numerous similar but smaller nodular masses. On the basis of the histologic appearance and immunohistochemistry results, a diagnosis of a germ cell tumor was made, with differential diagnoses including teratoma, dysgerminoma, choriocarcinoma and embryonal carcinoma. The possibility of a teratomatous twin was also considered; however, this was highly unlikely since only one embryo was transferred into the mare and confirmed viable via ultrasound at 45 days of gestation.

The foal was reported to be healthy until 52 days of age at which point she presented for a 5-day history of urine dribbling, intermittent fever, decreased nursing, hindlimb weakness,


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Keywords
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prolonged periods of recumbency and difficulty rising. The referring veterinarian attributed the urine dribbling to a suspected urinary tract infection, and administered one dose of ceftiofur crystalline free acid (dose unknown) the day prior to presentation and daily flunixin meglumine (dose unknown) for the 5 days prior. On presentation (Day 1) the foal (114-kg; 251-lb) was quiet, but alert and responsive with a rectal temperature of 38.9°C (102.0°F), heart rate of 120 beats/min and respiratory rate of 60 breaths/min; the foal was estimated to be 5% dehydrated. The foal was able to stand and walk, but severe bilateral ataxia and weakness (4/5) was present in the hindlimbs. Tail tone was absent, and urine was noted dribbling from the vulva. Anal tone was present, but depressed. The cranial nerves were intact, panniculus reflex was present bilaterally through all dermatomes and no obvious neurologic deficits were noted in the thoracic limbs. Neurologic deficits were localized to the lumbosacral region but no external evidence of trauma was present. Irregular raised lesions on the lateral aspect of the distal third metacarpal bone of the right limb and lateral portion of the distal third metatarsal bone of the left limb were also present. No heat was associated with these lesions, but pain was elicited with firm digital pressure.

A CBC revealed anemia (HCT 25.1%; reference interval, 31-44%), mature neutrophilia (10.03 x 10^9 cells/L; reference interval, 2.7-9.46 x 10^9 cells/L) and monocytosis (0.88x 10^9 cells/L; reference interval, 0.05-0.61 x 10^9 cells/L). Serum biochemistry analysis revealed increased activity of creatine kinase (CK, 1143 IU/L; reference interval, ≤ 426 IU/L), aspartate amino transferase (AST, 985 IU/L; reference interval, 20-484 IU/L), and gamma glutamyl transferase (GGT, 95 IU/L; reference interval, 0-38 IU/L). Hyperbilirubinemia (58.14 µmol/L; reference interval, ≤ 5 µmol/L) and hyperlactatemia (4.8 mmol/L; reference interval, ≤ 2.5 mmol/L) were also present. Resuscitative IV fluid therapy was initiated with a 2 liter bolus of isotonic fluids followed by one liter boluses of isotonic fluids, IV every 2 hours (105 mL/kg bw/tday). Gentamicin (6.6 mg/kg bw IV q 24 hours), flunixin meglumine (1.1 mg/kg bw IV q 24 hours) and omeprazole (4 mg/kg bw PO q 24 hours) were also administered.

The foal remained comfortable and on Day 2 was able to occasionally rise on her own to nurse; however, neurologic status was unchanged. Lateromedial and dorsoventral radiographs were performed of the thoracic, lumbar and sacral spine, revealing no evidence of vertebral fracture or malformation. Cerebrospinal fluid (CSF) was collected under light sedation (butorphanol tartrate 0.04 mg/kg bwt and diazepam 0.04 mg/kg bwt IV) from the lumbo sacral space and revealed marked elevation in total protein (214 mg/dL; reference interval, 32-48 mg/dL), pleocytosis (total nucleated cell count 30 cells/µL; reference interval, ≤ 5 cells/µL) and elevated RBCs (13,630 cells/µL; reference interval, 0 cells/µL). Cytologic evaluation of the CSF noted 66% neutrophils and 34% large mononuclear cells; large mononuclear cells occasionally contained phagocytized RBCs and cellular debris, consistent with pathologic hemorrhage. CSF was submitted for culture but yielded no bacterial growth. Increased activity of CK (4828 IU/L), AST (1088 IU/L), GGT (151 IU/L), and SDH (18.1 IU/L; reference interval, 1.1-4.6 IU/L) were present along with hyperbilirubinemia (57.80 µmol/L), hypoaluminemia (23 g/L; reference interval, 33-46 g/L), and hypoproteinemia (49 g/L; reference interval, 52-65 g/L) were measured on Day 2.

Due to the persistent elevations in hepatobiliary enzymes, an ultrasonographic examination of the abdomen was performed. Ultrasonographic abnormalities were limited to the liver, revealing numerous round heterogeneous masses of varying size diffusely distributed throughout the liver parenchyma; many of the masses were characterized by a thick hypoechoic rim that produced distal acoustic shadow artifact, consistent with mineralisation while the central portions were either solid tissue or anechoic, consistent with cavitation (Figure 2A). Transcutaneous liver biopsies subsequently documented a poorly differentiated neoplastic mass, suspected to be a teratocarcinoma on microscopic examination. Radiographs of the right metacarpophalangeal joint identified multifocal polyostotic regions of stippled lysis associated with the metaphysis and epiphyses of the third metacarpal bone and first and second phalanges (Figure 3A & B). A mild volume of spiculated periosteal new bone was associated with the distal metaphysis of the third metacarpal bone. Similar lysis was also noted in the navicular bone. These changes were consistent with osteomyelitis of hematogenous origin or neoplasia.

An indwelling nasogastric tube was placed to provide supplemental feeding (1000 mL mare's milk, q 3 hours) and antimicrobial therapy was continued. On Day 3, computed tomography of the abdomen and thorax were performed. Imaging revealed diffuse infiltration of the liver with distinctly marginated round masses that displayed hyperattenuating rims (100 HU) (Figure 4B). The centers of the masses were either hypointensating (20 HU) or heterogenously hyperattenuating (70 HU) compared to the remainder of the hepatic parenchyma. After contrast administration (Iohexol, 1.3 mL/kg bw t½), the margins of the masses became less distinct, and the remainder of the hepatic parenchyma enhanced heterogeneously rather than uniformly. Hypoattenuating centers of the masses did not contrast enhance suggesting tissue necrosis. CT also demonstrated multifocal regions of lysis affecting both femurs at their proximal and distal aspects, including the right femoral head, and both third metacarpal bones. Lysis was always associated with the metaphysis and epiphysis. Smooth periosteal reaction was noted at the ventrolateral aspects of the right eighth and left eleventh ribs with extrapleural soft tissue swelling associated with the 8th thoracic vertebra. In addition, a complete oblique sagittal fracture through the body of the first sacral vertebra was identified that extended through the ventral floor of the spinal canal (Figure 4C). The fracture was located right of midline with mild abaxial displacement of the fracture fragment. The primary differential for the hepatic changes was metastatic neoplasia. The hyperattenuating rims of the hepatic masses were considered to represent weak mineralization. As the polyostotic lesions of lysis, affecting all four limbs, were centered at the physes, bacterial osteomyelitis or neoplasia were differential diagnoses for the bony changes, including those noted on the ribs. Due to the grave prognosis the filly was euthanized.

At necropsy, a grossly enlarged and irregular liver along with multifocal bone lesions were observed. The liver weighed 6.8-kg
(15-lb) and had multifocal, irregular, raised nodules that were tan to yellow and often had central cavitations (Figure 4A). Nodules ranged from 0.5 to 3.0 cm in diameter and extended into the cut surface of the liver along with a large 10 cm diameter white mass within the liver. Upon examination of the vertebral canal and spinal cord, a fracture and osteolysis of the first sacral vertebral body was observed along with brown exudate within the spinal canal at the level of the lumbosacral junction. Bone lesions were also present on the 8th right rib, 11th left rib, and distal right third metacarpal, which upon cut surface revealed hyperostosis of the periosteum. Histologic examination of the liver, vertebral body, ribs, bone marrow cavities and distal metacarpal bone documented a mixed germ cell tumor, as a result of metastasis from the placental mass.

**DISCUSSION**

Evaluated individually, placental or hepatic neoplasia occurs infrequently in the horse. Examined in conjunction within one another, as in the case presented here, the presence of placental and disseminated hepatic neoplasia is an extremely rare clinical situation. A sparse number of published reports describe placental neoplasia in the horse and include teratocarcinomas and teratomas [1,2] Other considerations for placental nodules include trophoblastic diseases (hydatidiform mole, choriocarcinoma), germ cell tumors (dermoid cyst, dysgerminoma), metastatic tumors, granulomas and adenomatous hyperplasia of the trophoblast [1,3] Primary hepatic neoplasia in horses is also uncommon with hepatoblastoma being the most frequently reported in horses ranging in age from late-term aborted fetuses to 3 years [4]. Fewer reported cases of hepatic neoplasia exist in the foal, but published reports have described hepatoblastoma [5], hepatocellular carcinoma [6,7], mixed hamartoma [8] and mesenchymal hamartoma [4,9].

The case presented here is unique as it describes the clinical presentation, examination and diagnostic evaluation of a foal with placental metastasis of a germ cell tumor to multiple organ systems within the foal. Although rare, metastasis from the placenta to the fetus can occur via 2 general mechanisms: 1) maternal neoplasia that metastasizes to the placenta and then to the fetus (vertical transmission), or 2) primary placental neoplasia that metastasizes to the fetus [2,10-16]. The term vertical transmission does not apply to the latter because the placenta is considered a fetal structure [17]. Regardless of origin (maternal or placental), if neoplastic cells reach the fetal circulation; the fetal liver is the first organ to receive neoplastic cells via the umbilical vein. The opportunity for further dissemination of neoplastic cells outside the fetal liver is possible, and has been documented in other equine fetal or neonatal neoplasms that have metastasized to the brain, bone, lung and skin [18-20].

To the authors’ knowledge, this is the first documented case of a nonseminomatous germ cell tumor (NSGCT) in the horse. Germ cell tumors (GCT) arise from primordial cells and are subdivided into seminomas and NSGCT, with the majority of the latter in humans characterized by two or more cell types and wide dissemination [21,22]. Germ cell tumors are typically found in the gonads, with 90% of adult human GCT originating in the testes [21]. Additionally, these tumors comprise 3% of pediatric neoplasias [21,23]. While extragonadal locations are atypical in adult patients, approximately two thirds of pediatric GCT are extragonadal [21]. The embryologic development of these tumors likely predisposes towards the presence of tumors near mid-line as primordial cells migrate along the paravertebral gonadal ridge, leading to high prevalence of tumors in the sacrococcygeal region in children [21,23]. While the majority of sacrococcygeal tumors have an external component in children, the involvement of a sacral vertebral body in this case may support this pattern in the horse [21].

The etiology and pathogenesis of the neoplasia in this case is unknown, as is the exact time-line in the development of neoplasia in the foal. Germ cells form the foundational cells that follow one of several lines of differentiation and develop into the numerous fetal organs. Germ cell tumors arise from these primordial pluripotent germ cells and can thus represent a heterogeneous group of tumors [24]. The cause of germ cell tumors is not completely understood, but one theory suggests that they arise from aberrant or incomplete migration of primordial cells [25,26]. An alternate theory attributes tumor origin from pluripotent embryonal cells that have escaped the influence of embryogenic organizers controlling normal differentiation [25,26]. Regardless of the origin of the neoplastic cells in this case, the most likely theory in the development of the neoplasia ascribes that placental neoplastic cells first breached the fetus via the hematogenous route during gestation. Once neoplastic cells reached the fetal systemic circulation and the fetal liver, they disseminated to the skeletal system including the metacarpus, vertebrae, and ribs.

Interestingly, the presenting complaint in this case was urinary incontinence and hindlimb weakness, attributed to the sacral vertebral fracture prompted by neoplastic infiltration, rather than clinical signs related to the more morphologically obvious hepatic neoplasia. In general, metastatic bone lesions are not commonly associated with equine neoplasia [27,29]. The exact reason why the skeletal system was the only other system outside the liver infiltrated with neoplastic cells is unknown, but may be associated with tumor type [30]. In people, 80% of all skeletal metastatic lesions arise from prostate, breast or lung cancer and once present in the bone, typically cannot be cured [30,31]. When tumor cells invade bone, they secrete factors that affect both osteoblasts and osteoclasts, thereby disrupting normal bone homeostasis [30,31]. With some cases of skeletal metastasis, resorption of bone occurs more rapidly than bone formation resulting in osteolysis. Alternatively, in other types of cancer, tumor cells promote osteoblastic activity, thus forming more bone and resulting in bone proliferation. Interestingly, skeletal metastasis commonly promotes both osteolytic and osteoblastic components, which explains the osteolysis and bone fracture of the sacral vertebral with simultaneous hyperostosis of the ribs and metacarpus in the case presented here [30,31]. In addition to the obvious hindlimb paresis, intermittent fevers and lethargy were reported in this case, but other nonspecific clinical signs that have been reported in foals with hepatic neoplasia such as inappetence, weight loss, diarrhea and congestion of mucous membranes were not observed [5,18,32-35]. Clinicopathologic evidence of systemic inflammation and liver dysfunction were also observed in the case presented here, similar to previously reported cases of hepatic neoplasia [5,18,32-35]. Additionally,
abnormalities detected on CSF analysis reflected inflammation, pleocytosis and pathologic hemorrhage within the CNS most likely secondary to the sacral vertebral fracture. Although CSF analysis of foals with bacterial meningitis can result in similar CSF abnormalities as the foal described here, no bacterial growth was observed on CSF culture and necropsy examination did not support an infectious process [36].

A somewhat similar case of placental metastasis has been reported in a 10-week-old Arabian foal, although the tumor type was different than the case reported here [2]. In the previous report, a 5-year-old Arabian mare delivered a healthy, full-term colt, however, a mass was identified within the placenta, later determined to be a teratocarcinoma [2]. The foal presented again at 10 weeks of age for acute colic, abdominal distention, tachycardia and dehydration but died before any diagnostics were performed. Necropsy revealed disseminated multilobulated masses measuring up to 15 cm wide within the liver, omentum, spleen and sublumbar lymph nodes that were ultimately identified as a teratocarcinoma that had metastasized from the placental tumor [2]. In the previously reported equine case and the case presented here, the foals did not manifest clinical signs of neoplasia until 8-10 weeks of age and both cases had metastasis to various sites outside the liver. Neoplastic cells were likely present at birth in both foals, with the delay in manifestations of clinical signs corresponding to the growth of the neoplastic masses to a point of organ system decompensation in both cases: colic in the previously reported case and sacral vertebral fracture in the case presented here.

The case presented here describes a unique tumor and metastasis pattern that is rare in both humans and horses. Mixed germ cell tumors are uncommon in veterinary species with metastasis from the placenta to the fetus occurring even less frequently. While these neoplasms are rare, their occurrence presents a unique opportunity to further document metastatic neonatal neoplasms. Clinicians should be vigilant in examining and diagnosing placental masses, and realizing that in the rare case of placental neoplasia, the foal may be affected by neoplastic disease as well. Diagnosis in this case was aided by the use of thorough clinical examination of both the mare and foal, histopathologic evaluation and multiple imaging modalities.

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REFERENCES


