Doc Needs a Doc

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INTRODUCTION

Diseases of the spinal column and spinal cord may be due to a number of causes, including congenital defects, degenerative disease, neoplasia, infectious disease, injury or trauma, or vascular disease. In cats, disease most commonly arises from feline infectious peritonitis (7), spinal Lymphosarcoma, especially associated with feline leukemia virus (6), *Cryptococcus neoformans* infection, and occasionally Toxoplasmosis or spondylosis deformans. Injury and trauma are other common causes of spinal cord injury in the feline patient, and generally carry a poor prognosis. Rarer causes of spinal cord disease in cats include intervertebral disc disease, discospondylitis, and other tumors (7). Granular cell tumors (GCTs) have been reported frequently in human medicine, but are rare in veterinary species and exceedingly so in felines, with the first case being reported in 1989 (17). In human patients, these tumors present most commonly in the skin, head and neck, particularly the tongue, with other common sites including the respiratory tract, breast tissue, and gastrointestinal tract (15). However, GCTs of the nervous system are rare, presenting in both the peripheral and central nervous systems, having been reported in cerebral hemispheres, cranial nerves, and the spinal cord (13). Across multiple species, granular cell tumors have a similar histopathologic and immunohistochemical appearance and behavior (2, 10, 11). While the tumor itself is considered benign in nature, the location within the spinal cord and growth lend to a malignant behavior, leading to development of neurologic signs and decreased quality of life. However, the true malignant potential is unknown due to the rarity of GCTs. It is because of this rarity that any granular cell tumor experienced in practice should be reported to contribute to the literature.

HISTORY AND PRESENTATION

A 15-year-old male neutered domestic shorthair cat was presented to Mississippi State University College of Veterinary Medicine (MSU-CVM) Veterinary Specialty Center (VSC) on December 11, 2018 for evaluation of progressive paraparesis. The paraparesis was first noticed in July of 2018, and at that time was noted as mild and did not seem to progress until October, at which time the patient was presented to his primary care veterinarian, who prescribed prednisolone at 0.75 mg/kg once daily tapering dose. The patient initially improved, but the paraparesis returned and began to progressively worsen. On 11/29/18, the cat was unable to ambulate and became urinarily incontinent. On 12/05/18, he was re-presented to his primary care veterinarian, who prescribed gabapentin of an unknown dose and recommended referral to MSU-CVM, VSC. Prior to the paraparesis noted in July, the cat lived an indoor/outdoor lifestyle with three of his litter mates, with no previous health concerns.

Upon presentation to VSC, the patient was bright, alert and responsive. He was thin, with a body condition score of 3/9 and weighing 3.69kgs. His vital parameters were within normal limits, with a temperature of 100° F, heart rate of 200 beats per minute, and respiratory rate of 24 breaths per minute. Strong femoral pulses were noted in both pelvic limbs. His mucous membranes were pink and moist, with a capillary refill time of less than 2 seconds, indicating adequate hydration and perfusion. On abdominal palpation, a large and turgid bladder was noted, which was difficult to express. The area below his perineum and the caudal aspects of his legs were wet with urine. He was non-ambulatory paraparetic with hyperreflexia of the pelvic limbs, and muscle atrophy that was more significant over the right pelvic limb. Minimal to no motor was noted in the right pelvic limb, and minimal motor was noted in the left pelvic limb. A myoclonic gastrocnemius reflex was noted in the right pelvic limb. Withdrawal was reduced in the left pelvic limb, and absent in the right pelvic limb. The cutaneous trunci reflex stopped at

the level of T13 bilaterally. The remainder of the patient's physical and neurologic exams were within normal findings. Based on the neurologic findings, his lesion was localized to L4-S3 spinal cord segments, though diffuse disease cranially could not be fully excluded based on the hyperreflexia and myoclonic gastrocnemius reflex. A serum chemistry profile revealed an elevated BUN of 36 mg/dl (reference range 7-18 mg/dl) and elevated creatinine of 1.5 mg/dl (reference range 0.7-1.3 mg/dl). This azotemia was likely due to a combination of dehydration and urinary incontinence, though kidney disease was not completely ruled out at the time. Urinalysis showed a urine specific gravity of 1.014 (hyposthenuric) after receiving a 250-mL bolus of LRS fluids intravenously. A thyroid panel was submitted, and all values were within the normal range.

The patient was sedated with 0.2 mg/kg midazolam and 0.2 mg/kg butorphanol to perform radiographs, including a metal scan prior to magnetic resonance imaging (MRI), for which he went under general anesthesia with no complications noted. There was an irregularly-marginated, oblong, T2, T2 FS, STIR, contrast-enhancing intramedullary mass, measuring 4.6cm x 0.6cm x 0.5cm, and causing attenuation of the subarachnoid space from the level of the T6 to T10 vertebrae. The mass was hypointense on the T1 FLAIR sequence. There was an ill-defined, linear, T2 and STIR hyperintensity cranial and caudal to the region, and mild protrusion of the annulus fibrosis of multiple thoracic intervertebral discs. There was also decreased T2 signal intensity within the nuclei pulposi of multiple thoracic and lumbar intervertebral discs. Initial differential diagnoses for the mass included neoplasia (lymphoma), granuloma as a result of Toxoplasmosis or Neosporosis, and inflammatory disease. The hyperintensities cranial and caudal to the mass were potentially due to dilation of the central canal, or truncation artifact.

Upon admission to ICU, the patient was started on intravenous fluids (LRS 12 ml/hr) to correct dehydration and improve renal values, and prazosin (0.25mg PO q12h) for smooth muscle relaxation to facilitate ease in bladder expression. Blood pressure was regularly measured via Doppler to monitor for development of hypotension. All readings taken before and after prazosin administration were within normal limits and consistent throughout the patient's hospitalization. Within 24 hours, his renal values significantly improved and fluids were discontinued. The patient was also started on Clindamycin (12.5 mg/kg PO q12h) for empirical treatment of potential Toxoplasma infection. After thorough discussion with the owner regarding a full diagnostic work-up of the mass, including staging of potential neoplasia and prognosis, a complete investigation of the previously described spinal mass was pursued.

Thoracic radiographs revealed no evidence of nodular pulmonary metastatic neoplasia, but did show narrowing of multiple thoracic intervertebral disc spaces, likely consistent with spondylosis deformans, a normal degenerative change. Abdominal radiographs revealed no evidence of metastatic neoplasia in the abdomen. Narrowing of the L4-L5 intervertebral disc space with end plate sclerosis was noted, as well as enthetic new bone formation on the cranial margin of the pectin of the pubic bone. This was followed up with abdominal ultrasound to more accurately assess disease within soft tissue structures, which showed a diffusely enlarged and mildly hyperechoic liver with decreased conspicuity of the portal veins. There were multiple variably sized ovoid, smoothly marginated, hypoechoic nodules diffusely throughout the liver, with the largest measuring up to 1.39cm x 0.75cm. The spleen was diffusely hypoechoic, enlarged, and coarse in texture. The renal medullae were hyperechoic bilaterally, and the kidney margins were undulating bilaterally, with a mildly dilated left renal pelvis measuring up to 0.21cm. There was a moderate amount of hyperechoic debris within suspension in the urinary

bladder, and the pancreas was hypoechoic, containing multiple variably-sized and –shaped hyper- and hypoechoic nodules. There was also a scant amount of echogenic free fluid within the abdomen. Based on the appearance of the liver and spleen, fine-needle aspirates were collected of each.

The slides submitted from the liver showed moderate numbers of hepatocyte clusters, which occasionally had moderate numbers of cytoplasmic vacuolation typical of lipid accumulation. Low to moderate numbers of macrophages with erythrophagocytosis and leukophagocytosis were seen. Plasma cells were mildly to moderately increased. These findings were consistent with a moderate multifocal lipid accumulation, with possible lymphoplasmacytic inflammation of lymphoid hyperplasia. The slides from the spleen contained few splenic stroma clusters, and most of the lymphoid cells were normal-appearing small lymphocytes. Medium and large lymphocytes and plasma cell numbers were mildly to moderately increased, and there were low to moderate number of myeloid precursors throughout. These findings were most consistent with reactive lymphoid hyperplasia and mild splenic myelopoiesis. To further investigate any potential presence of lymphoma, an echocardiogram was performed. Mild aortic regurgitation was identified, which was likely a normal variant, but there were no other significant findings.

Upon finding no evidence of systemic spread of disease, a surgical biopsy of the spinal mass was elected. On December 14, the patient underwent general anesthesia for a right hemilaminectomy with durotomy at the level of T7-T8 in order to expose the spinal cord mass, perform a fine needle aspirate (FNA), impression smear, and if indicated due to a non-diagnostic FNA, incisional biopsy. Before samples were taken, swabs were collected to submit for culture and sensitivity. Both the fine needle aspirate and impression smear were read intraoperatively in order to determine the need for an incisional biopsy. The aspirate slides showed moderate

numbers of foamy cells that appeared to be lipid-laden macrophages, consistent with gitter cells. Fewer larger cells were seen, which had darker, foamy cytoplasm with round to oval nuclei. Anisocytosis and anisokaryosis were moderate, and nucleus to cytoplasm ratio was moderate. The chromatin was finely stippled and the cells had one large, prominent nucleolus. Direct impression smear was collected. The slides showed moderate numbers of nondegenerate neutrophils and low to moderate numbers of eosinophils. Few large round to stellate cells were seen. These cells had basophilic cytoplasm, and round to oval nuclei, interpreted as normal-appearing neurons. Because of the non-diagnostic aspirate and impression smear, an incisional biopsy was collected of the mass, under the spinal cord dura.

The biopsy specimens contained an expansive and infiltrative mass composed of tightly-packed, large, bland cells, which were round to slightly polygonal shape with abundant eosinophilic, moderately granular cytoplasm and round to ovoid, peripherally displaced nuclei with dispersed chromatin and one or more nucleoli. No mitotic figures were seen. Cells frequently had large, central eosinophilic areas surrounded by numerous small peripheral vacuoles, and the cytoplasm contained scattered small granules that were PAS-positive and diastase resistant. The cells were positive for vimentin, S100, and NSE, and were negative for CD18. Toward the margins of the sections were scattered foci of hemorrhage occasionally associated with neutrophils and fibrin. Based on the histologic appearance of abundantly eosinophilic and granular cytoplasm in polygonal cells, and the immunohistochemical staining characteristics, a diagnosis was made of meningeal granular cell tumor.

PATHOPHYSIOLOGY

Central nervous system granular cell tumors are well-reported in human medicine, but are extremely rare in cats. While these tumors initially were thought to be of myoblast origin, they

are recently considered to arise from meningeal tissue or specialized astrocytes (5). The most common site of presentation in humans is the head and neck, particularly the tongue, with a very small subset presenting in the spine (2). The distinction in development of intramedullary versus extramedullary tumors is unclear, although intradural-extramedullary tumors have been slightly more frequently reported. (2, 8, 12, 15). The malignant potential of these tumors is generally unknown, but no metastatic behavior has been reported. The histologic appearance of reported tumors is consistent with a benign nature. However, due to location and growth patterns, their behavior is considered malignant. One reported tumor in the digit of a cat was considered malignant (10).

Although a mass in the spinal cord may be histologically benign, the presence of the mass itself can lead to problems for the animal. An extramedullary mass is outside of the spinal cord parenchyma, and may be intradural or extradural. As the mass grows in size, it begins to compress the spinal cord and the nerve roots, leading to a slowly progressive onset of signs that will be referable to a focal lesion. An important differential diagnosis to a focal lesion within the spinal cord of a cat with slowly progressive signs is an infectious granuloma, due to either *Toxoplasma gondii* or *Neospora caninum*. Both of these organisms develop tissue cysts during their life cycle in the feline host, and when these develop in neural tissue can lead to development of neurologic signs such as ataxia, paresis, and ultimately paralysis (3, 4). Treatment of Toxoplasmosis consists of clindamycin and corticosteroid administration. Similarly, a less common but equally pathologic differential to consider is fibrocartilaginous embolism (FCE). Multiple theories exist regarding the development of FCE in the feline, including migration of disc material to the spinal arteries, persistence or neovascularization of

common blood supply to the spinal cord and intervertebral disc, or mechanical herniation of fibrocartilaginous material into the vertebral body (9).

DIAGNOSTIC APPROACH/CONSIDERATIONS

The majority of veterinary granular cell tumors reported have been diagnosed postmortem or have been incidental necropsy findings (10, 14, 17). Those cases in human medicine report patients presenting with lower back pain, intermittent limb numbness, and urinary and defecation difficulties (1). As with other suspect spinal cord masses, a T2-weighted MRI with contrast is the diagnostic imaging modality of choice. While MRI with contrast confirms the presence, location, and involvement of a spinal cord mass; definitive diagnosis requires a biopsy sample of the mass. However, due to the location, biopsy is rarely performed due to the risk of causing irreparable damage to the cord itself or the surrounding nerve roots. In previously reported canine cases of GCT, stereotactic biopsies from brain lesions were obtained under computed tomography guidance (5).

Diagnosis of granular cell tumor is based on histologic appearance and immunohistochemical behavior. Granular cell tumors are characterized by oval to polygonal cells of varying size (10). Cells will show distinct margins, eccentric nuclei, and abundant eosinophilic cytoplasm filled with PAS-positive and diastase-resistant granules (16). Cells will be positive for vimentin, S100, NSE, CD68, inhibin-α (1, 2, 10, 15), and negative for CD18, GFAP, neurofilament protein, HMB-45, keratin, EMA, CK7, chromogranin, and synaptophysin (5, 15).

TREATMENT AND MANAGEMENT

Due to the rare nature of granular cell tumors, and most lesions in veterinary medicine being diagnosed postmortem, treatment in veterinary species is relatively undiscussed and response to management is unknown. In human medicine, recommended treatment is surgical excision, occasionally followed by radiotherapy, though consideration is given to the location and involvement of the tumor itself (12). Research in canine patients with cranial masses has shown that radiotherapy is effective at reducing tumor size and neurologic signs, with minimal side effects (5, 6, 18). Patients may be medically managed, with adequate pain control and reduction of inflammation with corticosteroid administration, bladder management, and physiotherapy as needed depending on clinical signs.

CASE OUTCOME

The patient recovered uneventfully from surgery, and was continued on Clindamycin and Prazosin, while Buprenorphine (0.02 mg/kg IV q8h) and Gabapentin (10 mg/kg PO q8h) were added to his therapeutic regimen. His motor function and sensation were similar to his initial presentation in the immediate post-operative period, but appeared to wax and wane in the days following. Following the biopsy results, Clindamycin was discontinued, and prednisolone was started at a dose of 1 mg/kg, with a plan to taper over four weeks. Bladder management was continued, which consisted of prazosin administration approximately 2 hours prior to manual expression, performed at 6-hour intervals. He was placed in a wheelchair, which he tolerated very well for a feline patient. He was able to ambulate with his front limbs, and grew increasingly comfortable with the wheeled support. Due to the patient's clinical stability, and his owner's ability to manage his bladder at home, he was discharged on December 18, 2018. The patient went home with tapering instructions for prednisolone, another 10 days of Gabapentin, continuing prazosin, and a cart.

At the time of publication, approximately 12 weeks post-operatively, the patient was reported to be doing well and appears to have mild increase in the motor of his pelvic limbs. He tolerates the cart well, and goes on assisted walks. His bladder is still being managed. The owner has elected for continued palliative care.

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