River's Not Running Right

Tobi Ku Sones

Mississippi State University

College of Veterinary Medicine

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CPC Advisors: Ryan Gibson & Allison Mooney

Introduction

Canine spinal nephroblastoma (CSN) is a rare developmental neoplasm occurring in young dogs[1,2]. Presentation and clinical signs are consistent with a thoracolumbar myelopathy, and thus signalment and history are distinguishing diagnostic features of this disease.[1,2] Magnetic resonance imaging, computed tomography, and biopsy with histology are useful tools in the diagnostic approach towards suspected CSN.[1-6]

The prognosis for dogs with CSN varies widely and is primarily dependent on the elected treatment, which include palliative treatment of clinical signs, cytoreductive surgery, chemotherapy, and radiation.[1,2,5,7] Tumor location within the spinal cord is also associated with prognosis, as intradural-extramedullary tumors may have a median survival time (380 days) more than twice that of intramedullary tumor (140 days).[2] Multicentric or intraspinal metastatic CSN has been described in rare cases and are associated with a grave prognosis.[8,9]

This report describes a case of CSN occurring in a patient with representative signalment (age and breed predilection) and tumor location in which thorough diagnostics and management were pursued.

History and Presentation

River, a five-month-old 18.0-kg (39.6 lbs) intact female Labrador retriever, presented to Mississippi State University College of Veterinary Medicine (MSU-CVM) Neurology Service on August 25, 2020, for evaluation of a previously diagnosed spinal mass causing progressive weakness of the hindlimbs. Approximately three weeks prior to presentation, River developed right hindlimb weakness and an abnormal gait. Her hindlimb weakness rapidly progressed and she became non-ambulatory paraparetic. She presented to her primary care veterinarian on

August 13, 2020, where magnetic resonance imaging (MRI) was performed and revealed an intradural spinal tumor at the level of T11 and T12. River was referred to MSU-CVM on suspicion of CSN. Clindamycin (9 mg/kg orally every 12 hours) and methylprednisolone (40 mg intramuscular injection) were administered at the time of the MRI for empirical treatment of potential infectious or inflammatory etiologies until the scheduled referral appointment.

On presentation to the Veterinary Specialty Center, River was bright, alert and responsive. She was unable to rise in her hindlimbs. On physical examination, she had an ideal body condition score of 5 out of 9. Her vital parameters were within normal limits with a body temperature of 102.1 degrees Fahrenheit, heart rate of 120 beats per minute, and panting respiratory rate. Her mucous membranes were pink and moist with a capillary refill time of less than 2 seconds and no prolonged skin tent, indicating adequate hydration. On cardiopulmonary auscultation a normal sinus arrhythmia was ausculted and no murmurs, crackles, or wheezes were heard. She had strong, synchronous femoral pulses.

Upon neurological evaluation, River was non-ambulatory with severe paraparesis. Motor control of the hindlimbs was limited to hip flexion and hindlimb proprioception was absent, but normal sensation was present. She had normal withdrawal and segmental reflexes in all four limbs and did not appear painful. All cranial nerve responses appeared normal. Her neuroanatomical localization was thoracolumbar, between T3 to L3 spinal cord segments. Her urinary bladder was easily expressed when pressure was applied to her abdomen. Since her urine was malodorous, a sample was collected for testing by ultrasound-guided cystocentesis.

Diagnostic Approach

As River's clinical signs were consistent with a thoracolumbar myelopathy, spinal MRI had been performed prior to referral. This report revealed an intradural mass that appeared extramedullary; however, intramedullary localization could not be fully excluded. Cerebrospinal fluid (CSF) tap was also performed at the time of the MRI but cytology found no clinical abnormalities. CSF was submitted for analysis and found to be negative for toxoplasmosis. In cases of CSN, CSF analysis is unlikely to be specific nor diagnostic. Instead, biopsy of the spinal cord mass with histology and immunohistochemistry is most helpful for distinguishing CSN from other primitive spinal cord tumors.[1,2,5,7]

Computed tomography (CT) imaging was performed at MSU-CVM Veterinary Specialty Center for surgical planning. Contrast CT images were also obtained following intravenous administration (30 mL) of gadodiamide solution (Omniscan, GE Healthcare, Paramatta, Australia). The CT scan findings were consistent with a thoracolumbar intramedullary compressive myelopathy. A smoothly marginated, ovoid, homogenously-contrasting, soft-tissue opaque structure was visualized causing approximately 95% attenuation of the spinal cord, spanning from the caudal aspect of T11 to the cranial aspect of T13. Possible differential diagnoses for this mass included CSN, lymphoma, ependymoma, primitive neuroectodermal tumor, or granulomatous etiologies such as toxoplasmosis.[1, 2] In dogs, one-third of spinal tumors are located intradural and extramedullary, with meningiomas and nerve sheath tumors being most common.[6]

Venous blood samples were submitted for complete blood count and chemistry panel. The chemistry revealed mildly elevated alanine transaminase (93 U/L), mildly elevated calcium (12.0 mg/dl), and moderately elevated phosphorus (5.8 mg/dl), along with mildly decreased osmolarity

(280 mOsm/kg), which were clinically insignificant. Complete blood count results were unremarkable.

Urinalysis and urine culture and sensitivity were submitted on suspicion of a urinary tract infection. The urine sample appeared slightly hazy and had a urine specific gravity of 1.034. Moderate bacteriuria, hematuria (1-5 RBC) and leukocyturia (10-25) were seen. *Escherichia coli* (>100,000 cfu/ml urine) was cultured and determined susceptible to amoxicillin-clavulanic acid, ampicillin, enrofloxacin, tetracycline and trimethoprim-sulfa antibiotics.

Pathophysiology

CSN is a tumor of young dogs that invades the spinal cord and causes compressive myelopathy, with large-breed dogs such as German Shepherds and Retriever breeds predisposed and no known sex predisposition.[1,2] There has been no known exploration of possible fetal or maternal risk factors. While these tumors are typically regarded as non-malignant with absence of a primary renal tumor, rare multicentric or metastatic cases have been described.[8.9] Also known as Wilms' tumor, nephroblastoma is one of the most common intrabdominal tumors of human children, although this is distinct from the ectopic spinal form.[10] The term "blastoma" refers to the embryonic, immature origin of the malignant counterpart, as this neoplasm uniquely affects young animals.[4]

On histopathology and cytology, CSN are considerably similar to both renal nephroblastoma and primordial renal tissue with a triphasic pattern consisting of cuboidal and columnar epithelial cells populations arranged into tubule- and glomerule-like structures; polygonal blastema cells with large, abnormal nuclei arranged into nests; and indistinct, poorly-differentiated spindle cells in irregular arrangement.[4,5] Immunohistochemistry staining allows for definitive differentiation

of nephroblastoma from other spinal tumors with primitive cell populations. Nephroblastoma cells are uniquely characterized by positive staining for both cytokeratin (epithelial cell marker) and vimentin (mesenchymal cell marker), as the cell populations are so primitive they have not yet differentiated between epithelial and mesenchymal cell lines.[1,5] The WT-1 antibody (Wilms tumor 1 protein, a human nephroblastoma gene product) special stain is also commonly used to distinguish CSN from other spinal tumors.[1,5] Antibody reaction to polysialic acid, found in embryonic kidney cells and human renal blastoma, has been explored as another applicable positive immunoreactivity test.[2] In contrast, negative staining for cytokeratin is supportive of ependymoma, and positive staining of GFAP (glial fibrillary acidic protein) is consistent with primitive neuroectodermal tumor.[1] These histologic descriptions and immunohistological characteristics support the idea that CSN originates from metanephric blastema, undifferentiated cells of renal origin, that become trapped in the spinal cord during mesenchymal development and remain inappropriately sequestered beyond fetal maturation.[1,8]

Treatment & Management Considerations

Treatment options for CSN include palliative treatment of clinical signs, cytoreductive surgery, and radiation. Due to the uncommon prevalence of CSN, a treatment of choice has not been determined through controlled experimental trials. Surgical resection of the tumor, also known as cytoreductive surgery, is associated with improved outcomes compared to palliative treatment. One study of 11 affected dogs described a 70.5-day mean survival time following cytoreductive surgery.[1] Another study of 10 affected dogs reported a median survival time of 374 days with surgery or radiotherapy treatment.[2] In contrast, palliative treatment alone was associated with median survival time of 55 days.[2] Repeated cytoreductive surgery has also been

documented in one case where clinical signs returned twelve months after initial surgery and improved again for five months following a second surgery.[11]

Surgery along with radiation therapy appears to yield the best prognosis in terms of survival time, limb function, and ambulation. Cytoreductive surgery and external beam radiation therapy preserved neurological function of one dog with ambulatory asymmetric paraparesis (worse in left pelvic limb); at publication 1 year and 2 months after surgery, this patient's condition had improved to strongly ambulatory, mild paraparesis of the left pelvic limb with normal right pelvic limb.[5] Another study of a spinal nephrectomy patient who underwent cytoreductive surgery and radiation therapy demonstrated curative treatment of the nephroblastoma with survival time of 5 ½ years following initial diagnosis, but also documented radiation-induced osteosarcoma as the cause of eventual euthanasia.[7] While this remains a potential adverse effect of radiation therapy, careful consideration of radiation fractionation schemes used in young dogs such as those with nephroblastoma can be useful in managing these risks.[2,7]

Regardless of the underlying cause, dogs with thoracolumbar spinal cord injury are prone to persistent lower urinary tract dysfunction consisting of both inappropriate urine storage with leaking and inefficient urine voiding with high residual volume.[12] These abnormalities can persist for months or be lifelong and can affect both quality of life and life expectancy, especially since urinary tract infections commonly occur and can progress to pyelonephritis.[12-14] Significantly increased risk of urinary tract infection is associated with female dogs, non-ambulatory status, lack of voluntary urination ability, absence of perioperative cefazolin, and perioperative hypothermia (<95 degrees Fahrenheit).[13] Ongoing bladder management is needed to reduce the risk of detrusor muscle atony and urinary tract infection, and this is achieved by monitoring urinary bladder measurement and volume quantification; bladder expression and

intermittent or indwelling urinary catheter placement; pharmacotherapy aimed at modulating the micturition pathway; and antibiotic therapy for urinary tract infections informed by culture and sensitivity.[12] If in-dwelling urinary catheterization is used to manage neurogenic urinary dysfunction, the duration of use should be minimized due to higher risk of ascending infection.[15,16]

Case Outcome

On August 26, 2020, River underwent a right-sided hemilaminectomy with durotomy under general anesthesia. Anesthetic induction was performed with propofol and midazolam and she was maintained under isoflurane inhaled anesthesia, fentanyl continuous rate infusion, and lidocaine continuous rate infusion during the procedure. During surgery, cefazolin was administered (22 mg/kg intravenously every 90 minutes) for perioperative infection prophylaxis. River was sterilely prepped and aseptically draped in the operating room. A dorsal midline incision was made over the spinous processes from T10 to L1. Blunt and sharp dissection of subcutaneous tissues and fascial planes was performed to the level of the vertebral bodies and articular facets of T10-T11-T12-T13-L1. The vertebral bone was removed with a pneumatic burr, Lempert rongeurs, and Kerrison rongeurs allowing access to the vertebral canal at the level of T10 to T13. The margins of the tumor within the spinal cord was identified visually and a #12 surgical scalpel blade was used to perform a durotomy cranial and caudal to the margins of the tumor. The tumor was carefully removed using a series of microinstruments including a blunt round-tipped probe, ball-end-ball probe, forceps, surgical spears, and small suction tip. Samples of the tumor were saved and preserved in formalin for histopathology submission. The spinal cord was visualized and appeared thin and compressed, as suggested by the previous imaging.

The surgical site was copiously lavaged using sterile saline. Gel foam was placed on the cranial and caudal margins of the hemilaminectomy site to provide scaffolding followed by a fat graft that was obtained during initial dissection and preserved in saline-moistened gauze for the duration of the procedure. The dorsal lumbar fascia, subcutaneous and fat tissues, and epidermis were closed routinely. An indwelling urinary catheter (Foley catheter, MILA International Inc., Florence, Kentucky) was placed under anesthesia. Packed cell volume and total protein were assessed at the end of anesthesia and found to be normal (45%; 6.0 g/dL). Recovery from surgery and anesthesia was uneventful.

River was hospitalized for 14 days following surgery. Her urinary catheter remained patent and was removed 2 days post-operatively; thereafter, her urinary bladder size was measured on abdominal ultrasound every 6 to 8 hours and expressed when measured to be over 10 mL/kg. She was prescribed amoxicillin (11 mg/kg orally every 12 hours) for urinary tract infection; trazodone (3 mg/kg every orally 8 hours) for activity restriction and anxiolysis; omeprazole (1 mg/kg orally every 12 hours) as a gastroprotectant; Tylenol 4 (acetaminophen and codeine, 1.6 mg/kg orally every 8 hours) and gabapentin (10.9 mg/kg orally every 8 hours) for postoperative pain control; and diazepam (0.5 mg/kg orally every 8 hours), bethanechol (5 mg orally every 8 hours), and prazosin (1 mg orally every 9 hours) for neurogenic bladder management.

A seroma associated with River's incision site was detected on physical examination 7 days after surgery. It was presumptively associated with River's high activity level and underwater treadmill sessions. For the remainder of her hospital stay, heat therapy was applied to the seroma site using a warm pack 3 times daily, however the seroma continued to increase in size. River had several mild episodes of bilious vomiting at 8 days and 11 days post-operatively, which improved with increased meal frequency and administration of all medications with food.

River was fitted for a mobility cart (Walkin' Wheels rear dog wheelchair, Walkin' Pets, Amherst, New Hampshire) 3 days post-operatively and began physical therapy sessions with the MSU-CVM Rehabilitation Service 6 days post-operatively. She had a total of 7 physical therapy sessions with the goals of maintaining hindlimb strength, improving hindlimb mobility, and minimizing muscle atrophy. During these sessions, River underwent physio exercise ball standing with weight shifting and rear leg withdrawal reflex instigation; underwater treadmill walking; neuromuscular electrical stimulation; and cart walking with hindlimb therapy resistance bands.

Histopathological assessment of River's intra-operative spinal cord mass biopsy was performed by MSU-CVM Diagnostic Laboratory service, with a finalized report produced on August 28, 2020. The samples were composed of primitive mesenchymal neoplastic cells that formed structures loosely resembling embryonic tubules and glomeruli. Although immunohistochemical staining was not performed, these descriptive findings were consistent with a well-differentiated nephroblastoma. Nuclear changes were limited, with a mitotic rate of 1 per high-powered field in addition to minimal anisocytosis and anisokaryosis. Full excision of the nephroblastoma was not confirmed, as neoplastic changes extended to all surgical margins.

River was discharged from the hospital on September 9, 2020. At discharge, she was non-ambulatory paraparetic with improving motor control. Due to proximity to the owner's location, River was referred to Auburn University College of Veterinary Medicine Oncology Service for radiation therapy. Over the course of her therapy, she received a total radiation dose of 48 Gray consisting of 16 fractions of 6 Mega-volt photons of 3 Gray each from a clinical linear accelerator. River completed her final radiation session on October 9, 2020. At the most recent follow-up communication, River's owners indicated that she has been doing well in her mobility

cart, her hindlimb function has significantly improved, she is continuing to improve in her ability to urinate and defecate normally, and she is able to stand on her own for short periods of time.

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