Dixie's Descent

Myelomalacia: A Detrimental Sequela Following Intervertebral Disc Herniation

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Introduction

Myelomalacia describes gross softening of the spinal cord, with loss of distinction between gray and white matter histologically. Myelomalacia is usually characterized by hemorrhagic necrosis and liquefaction of the spinal cord tissue and can be associated with any type of spinal cord injury, including intervertebral disc herniation. Myelomalacia can be classified as focal, ascending, or descending. Following intervertebral disc herniation, it can develop hours to several days later and in some cases even up to 2 weeks. There is no treatment for myelomalacia. If myelomalacia progresses cranially from the site of initial spinal cord injury, patients will succumb to respiratory compromise and ultimately failure if not euthanized.

History and Presentation

Dixie was an approximately 6-year-old female spayed Boston Terrier mix who presented to MSU-CVM's Emergency service late in the evening on June 26, 2018 for evaluation of being acutely down in the hind end since 5:30 p.m that day. She had reportedly been completely normal that morning, with no recent or past history of neurological deficits. On presentation, Dixie was bright and alert but was very anxious and painful. All vital parameters were within normal limits. Neurological examination revealed that Dixie was paraplegic with a Schiff-Sherrington posture. All cranial nerves were intact. Proprioception was absent in the pelvic limbs. Reflexes were normal in all limbs, and her cutaneous trunci reflex was present in the mid- to caudal lumbar region. Nociception (deep pain sensation) was intact in both pelvic limbs. Dixie's neurological exam was consistent with a T3-L3 myelopathy. She was admitted to the hospital for transfer to the Neurology service the following morning and was maintained on a

fentanyl CRI and Cerenia overnight. Around 4 a.m. on June 27th, Dixie progressed to being deep pain negative in both pelvic limbs.

A complete blood count (CBC) and chemistry panel were performed. The CBC showed a mild lymphopenia and monocytopenia, consistent with a stress leukogram, but was otherwise unremarkable. Chemistry panel revealed a mild hypernatremia and severe elevation in creatinine kinase (CK). Urinalysis was unremarkable, and urine culture was negative. Thoracic radiographs performed on the morning of June 27th revealed a mild, diffuse, bronchial pulmonary pattern but no evidence of pulmonary metastatic disease. Thoracolumbar computed tomography (CT) was then performed and revealed a left-sided, extradural, compressive myelopathy at T12-13 due to extruded intervertebral disc material. Dixie was promptly taken to surgery for a left T11-12-T13-L1 hemilaminectomy with fenestration of T11-12, T12-13, T13-L1, and L1-2 to remove the extruded disc material and decompress the spinal cord. Grossly, the spinal cord was noted to be severely bruised and discolored intraoperatively. There were no surgical complications and recovery from anesthesia was uneventful. An indwelling urinary catheter was placed post-operatively.

Pathophysiology

Progressive myelomalacia is perhaps the most worrisome sequala following intervertebral disc herniation or other severe spinal cord injury. The most common location for disc herniation in small breed dogs who developed progressive myelomalacia in one study was T12-T13, but mid to caudal lumbar herniations were also noted, specifically between L4 and L5[2]. Patients whose neurologic status rapidly deteriorate may be indicative of the severity of spinal cord injury and may further lead to the progression of myelomalacia. Dogs who display

clinical signs for less than 24 hours prior to presentation were 3.54 times more likely to develop progressive myelomalacia than dogs whose signs were present for greater than 24 hours[2]. However, this is not always the case, as myelomalacia may also been seen in patients who experience a gradual onset of clinical signs. Therefore, dogs with a gradual onset of signs should not be considered to be at a decreased risk of developing myelomalacia.

Any traumatic insult to the spinal cord involves a primary mechanical damage to the parenchyma, which then leads to secondary damage. In cases of myelomalacia secondary to acute intervertebral disc extrusion, the primary injury and initial driving force is caused by direct spinal cord compression from the extruded intervertebral disc material, which increases intraspinal pressure and causes ischemia[1,2]. There is also evidence that extrusion of disc material may be involved in the extension of spinal cord liquefaction. The combination of cerebrospinal fluid and hemorrhagic debris is thought to facilitate longitudinal spread of necrotic debris[1]. Specifically, subdural and intramedullary hemorrhages are thought to be involved in the progression of spinal cord destruction[6]. Hemorrhage is considered to be a consequence as well as a contributing factor to the progression of traumatic myelomalacia. The biochemical effects of blood on spinal cord tissue are thought be detrimental as well[7].

Secondary damage to the spinal cord in myelomalacia, ultimately resulting in cavitation of the gray and white matter, is caused by decreased vascular perfusion of the spinal cord, due to electrolyte shifts, specifically the influx of sodium and calcium.[4] Increased concentrations of intracellular calcium lead to the activation of phospholipase A2, which triggers the inflammatory cascade. Calcium binds to phosphates, which depletes ATP. This leads to mitochondrial dysfunction, the development of cytotoxic edema, and neuronal cell death via apoptosis. Multiple biochemical factors favor the production and release of free radicals, which further

perpetuate ongoing cellular injury and necrosis. Cellular enzymes and vasoactive substances arachidonic acid and nitric oxide, respectively, contribute to microvascular thrombosis and further spinal cord ischemia secondary to traumatic injury[4] . These processes can occur within hours of the primary injury.

The histopathological appearance of myelomalacia was first described in 1972[5]. It is characterized by severe thrombosis and hemorrhage within the spinal cord parenchyma, which is often associated with contusive and/or compressive spinal cord injury. It can occur as a focal lesion, confined to the epicenter of initial spinal cord injury[6]. Other times, however, myelomalacia may spread either cranially (ascending) or caudally (descending) from the site of initial damage. Clinical signs of descending myelomalacia include progressive lower motor neuron signs, namely decreased to absent muscle tone and reflexes in the pelvic limbs, loss of abdominal tone, decreased to absent tail tone, and loss of anal tone. Clinical signs of ascending myelomalacia include cranial advancement of the cutaneous trunci muscle reflex and eventually paralysis of respiratory muscles and thoracic limbs[1]. Elevated body temperature and diffuse hyperesthesia (not always localized to the spine) are also indicative of progressive myelomalacia. These signs may be triggered by systemic disease or brain involvement.[1]

Diagnostic Approach

At present, the gold standard for diagnosis of myelomalacia is necropsy. However, certain diagnostic findings can be highly suggestive of myelomalacia and therefore useful antemortem. Magnetic resonance imaging (MRI) is the imaging modality of choice for the diagnosis of intraparenchymal spinal cord disease in companion animals, with T2 weighted sequences regarded as most helpful in predicting myelomalacia. A T2-weighted hyperintensity

six times the length of the L2 vertebral body may be indicative of myelomalacia, but does not always preclude the progression of myelomalacia[2]. T2-weighted MRI sequences have been previously reported to be useful in correlating imaging lesions to histopathologic lesion severity[6]. Other studies have indicated that MRI findings in conjunction with cerebrospinal fluid (CSF) analysis may be able to detect progressive myelomalacia prior to clinical diagnosis. Secondary changes to cerebrospinal fluid composition in progressive myelomalacia may include xanthochromia, pleocytosis, and increased protein, which would result in an inhomogeneous fluid and lengthen T2 relaxation time, thus decreasing CSF signal intensity on MRI[5]. Detection of CSF composition changes within the subarachnoid space can be evident on a single-shot turbo spin echo (SSTSE) sequence. Compared to standard weighted T2 images, SSTSE easily detects cerebrospinal fluid intensities by suppressing the signal from all other tissues, allowing abnormal intensities from CSF to be more conspicuous[5]. In one study, SSTSE was used to evaluate cerebrospinal fluid signal loss in deep pain negative dogs. Dogs that developed progressive myelomalacia had extensive loss of CSF signal on SSTSE sequences compared to those that did not[5]. Dogs whose ratio of length of CSF fluid attenuation to the length of L2 vertebral body on SSTSE sequences was less than 7.4 were unlikely to develop myelomalacia; however, the prognosis in dogs with higher ratios (greater than 7.4) could not be determined. Specific MRI findings such as these may help to diagnostically identify populations of deep pain negative dogs with poorer prognoses, particularly those that carry a higher risk for developing myelomalacia. Measuring serum levels of glial fibrillary acid protein (GFAP), a major constituent protein of mature astrocytes, using an ELISA test is highly specific (97.7%)[2]. This test may also be useful in antemortem diagnosis of myelomalacia, however, it does not have a rapid enough turnaround time to be practical in the clinical setting.

Myelography can also be used in the diagnosis of myelopathies, and specific myelography findings have been correlated with the presence of myelomalacia. There are four basic myelographic patterns: normal, extradural, intradural/extramedullary, and intramedullary. Intervertebral disc extrusions are the most common cause of extradural myelographic patterns. An intradural/extramedullary pattern is produced when a lesion is within the subarachnoid space (intradural), but not invading the parenchyma of the cord (extramedullary); this is most commonly seen with neoplasia. An intramedullary pattern can be seen with spinal cord edema and trauma. In addition to apparent spinal cord swelling, contrast leakage into the spinal cord parenchyma may be appreciated in cases of spinal cord myelomalacia.[3] Myelogram findings in myelomalacia were reported as variable in one study. Dogs with focal myelomalacia following fibrocartilaginous embolism were identified as having an intramedullary pattern due to spinal cord swelling. However, dogs who had intervertebral disc protrusion with subsequent myelomalacia subsequent also had spinal cord swelling. Contrast medium infiltration was observed in most dogs with myelomalacia and varied from subtle to extensive. Focal contrast infiltration was seen in dogs with both focal and diffuse myelomalacia. The most marked infiltration of contrast medium was seen with the most marked spinal cord swelling in a dog with diffuse myelomalacia. The more marked the swelling and infiltration of contrast medium, the poorer the prognosis.[9] In conjunction with history and clinical signs, CT combined with myelography may have a greater sensitivity for identifying myelomalacia by improving detection of intramedullary contrast medium accumulation

Treatment and Management

There is no treatment for myelomalacia once it has developed, so intervention is aimed at prevention. Identifying risk factors facing dogs who suffer from acute intervertebral disc

herniation or other contusive spinal cord injuries is important for both therapeutic planning and prognostic assessment. Although the timing of surgical intervention was once thought to be a major determinant of outcome in dogs lacking deep pain perception, more recent studies suggest that these patients may have a fixed prognosis at the time of injury related to characteristics of the injury itself. Onset of paraplegia, decompressive surgery, or corticosteroid drug administration had no effect on prognosis within a 3-month follow-up period in one study[6]. In this study, dogs who experienced paraplegia with loss of deep pain perception for greater than 48 hours had no poorer prognosis than those of less than 48 hours. However, dogs who showed neurological signs for less than 24 hours prior to presentation to the veterinarian were over three times more likely to develop progressive myelomalacia compared to dogs who displayed signs for greater than 24 hours prior to presentation. Severity of spinal cord compression and temporal factors, specifically duration of clinical signs before onset of paraplegia and delay between onset of clinical signs and referral evaluation, may not affect overall prognosis as was once thought.

The prevalence of progressive myelomalacia in dogs with thoracolumbar intervertebral disc herniation ranges from 0 to 14.5%, with an average of 2%.[1] The prevalence in dogs with absent nociception was shown to be slightly higher, ranging from 9 to 18%. Dogs with more severe neurological deficits (high grade of 3,4, or 5 out of a 5-point scale) are more likely to develop myelomalacia. Ten percent of dogs in one study that underwent surgical repair of acute intervertebral disc extrusion developed ascending myelomalacia[6]. Additionally, some dogs with intervertebral disc herniations at L5-L6 may be at increased risk for developing myelomalacia[1]. Although the precise reason for this remains unknown, it is theorized to be related to the blood supply to the spinal cord in this region. The great radicular artery enters the spinal cord in the region of L5-6 and supplies 2/3rd of the ventral blood supply caudal to L5, as well as a significant

portion of the ventral blood supply cranial to L5. Spinal cord injury both directly damages the vasculature and indirectly propagates damage by way of biochemical processes. Despite changes in systemic blood pressure, spinal cord blood flow is designed to remain constant. However, autoregulatory mechanisms fail in the face of spinal cord damage. In these cases, prolonged systemic hypotension can lead to decreased spinal cord blood flow and, ultimately, ischemia. During intervertebral disc herniation, damage to the great radicular artery is thought to cause a large area of spinal cord ischemia and subsequently necrosis. Gray matter is most commonly affected because it is more metabolically active compared to white matter due to its high lipid content. Secondary factors, such as ischemia-reperfusion phenomena and the presence of hemorrhage (causing elevated levels of iron and copper) as well as the composition of the spinal cord tissue itself, further perpetuate injury by encouraging production of reactive oxygen species furthering cell injury and necrosis.[3]

Case Outcome

On the evening of June 27th, approximately 9 hours post-op, Dixie appeared uncomfortable in her cage and was vocalizing; her pain score at that time was 10/20. Her rectal temperature was also markedly elevated at 106 degrees Fahrenheit. She was administered a bolus of isotonic crystalloid fluids and an intravenous dose of dexmedetomidine. Her fentanyl CRI was also increased for improved pain control, and a fan was placed in front of her cage. She was noted to be resting comfortably approximately one hour later. The following morning, on June 28th , Dixie was less restless and had a normal rectal temperature. Her neurological exam was static, compared to pre-operatively; she was paraplegic with absent deep pain sensation but had normal reflexes and muscle tone in the pelvic limbs. On June 29th, 2 days post-op, Dixie

remained paraplegic with absent deep pain sensation but was also noted to have absent anal tone, hypotonic pelvic limbs, and an increasing rectal temperature. Based on these changes, there was significant concern for progressive myelomalacia. By that evening, she was unable to support herself in the thoracic limbs, had poor abdominal muscle tone, and had developed a paradoxical breathing pattern. Humane euthanasia was recommended and elected due to concern for impending respiratory decompensation.

Post-mortem evaluation of the spinal cord revealed gross evidence of myelomalacia from T10 to L2, with extensive subdural hemorrhage extending further cranially to the brain. Histopathology revealed expansion of the subdural and subarachnoid spaces by a variable amount of blood. Most prominent in the lower cervical (C5) and lumbar (L4) spinal cord segments, there were variable degrees of axonal degeneration, as the axons were swollen within dilated myelin sheaths. Evaluation of longitudinal sections revealed evidence of digestion chambers containing scattered debris and occasional gitter cells. In the T5 spinal cord segment, there was diffuse loss of spinal cord architecture with rarefaction, fragmentation, and vacuolation of the neuropil, accompanied with a large amount of hemorrhage. There was loss of white-grey matter delineation, and the neurons were shrunken with loss of Nissl substance and occasional peripheralization or loss of nuclei. There was multifocal perivascular cuffs of mostly neutrophils, with fewer lymphocytes and macrophages.

Ultimately, euthanizing Dixie was unquestionably the most humane decision. Post-operatively she exhibited clinical signs consistent with progressive myelomalacia, both ascending and descending. Had her spinal cord damage continued to ascend, her cutaneous trunci reflex would have been expected to move further cranially. With extension of myelomalacia to the level of the C6-T2 spinal cord segments, her thoracic limbs would have eventually become

paralyzed. Her inability to support herself in the thoracic limbs shortly before euthanasia suggests that these spinal cord segments were already becoming affected. Patients with progressive myelomalacia often become febrile and uncomfortable, as did Dixie, due to this disorder causing a massive inflammatory response. Finally, respiratory paralysis would have ensued with further spread of the lesion spread to involve the C3-C5 spinal cord segments, which give rise to the phrenic nerve innervating the intercostal muscles and diaphragm.

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