“Maverick Has a Bogey on His Six”

Anaplastic Sarcoma in a Great Dane

Anna Hubbell

Mississippi State University College of Veterinary Medicine

Class of 2020

Clinicopathologic Conference

February 21, 2020

Advisor: Michaela Beasley, DVM, MS, DACVIM (Neurology)

Introduction:

Canine soft tissue sarcomas arise from mesenchymal tissue and are grouped together based on similar biological behavior. These tumors infiltrate along fascial planes, metastasize hematogenously and are locally invasive[12]. Sometimes the tissue of origin cannot be determined for these tumors, and they are classified as anaplastic or undifferentiated sarcomas. Anaplasia refers to a lack of differentiation in cells. These anaplastic cells often have prominent nucleoli, a hyperchromatic nucleus, a nucleus to cytoplasm ratio of approximately 1:1 and have high mitotic rates[7]. Anaplasia in neoplastic cells often indicates highly aggressive lesions. For all soft tissue sarcomas regardless of the tissue of origin, surgical excision is often the cornerstone of treatment protocols[8]. In areas where wide surgical margins cannot be obtained, radiation may be used, and chemotherapy may be used when metastasis is present or likely[12]. Prognosis is influenced by histological grade, size of the tumor, fixation to surrounding tissues, presence of metastasis and completeness of surgical margins[8].

History and Presentation:

Maverick is an approximately 2-year-old male neutered Great Dane who presented to MSU-CVM Neurology Service on 6/28/19 for being acutely down in his hind limbs. He presented to his rDVM on 6/24/19 for trouble urinating. His owners noted that when Maverick would try to urinate, he would seem uncomfortable and had trouble posturing to urinate. A complete blood count (CBC) revealed a mild stress leukogram, and a serum chemistry revealed a mild hyperglycemia. He was presumptively diagnosed with a urinary tract infection and sent home on Clavamox® and Rimadyl®. Maverick's signs did not improve on these medications, and he presented again to his rDVM on the morning of 6/28/19. Another CBC was performed revealing a moderate granulocytosis, and his serum chemistry revealed a mild hyperglycemia.

Radiographs were taken of the thorax, abdomen and pelvis. These radiographs did not reveal the presence of radiopaque urinary calculi or radiographic changes consistent with osteoarthritis of the hips. Maverick's clinical signs worsened throughout the day and he was referred to MSU-CVM Neurology services at this time. His owners noted that he was still ambulatory the morning of 6/28/19, but that he progressively became more lame in his hind limbs throughout the day and became non-ambulatory that afternoon.

On presentation, Maverick was bright, alert and responsive. He was tachycardic with a pulse of 108 bpm and a grade 3/5 holosystolic heart murmur was heard on auscultation of the heart. His mucous membranes were pink and moist with a CRT of less than 2 seconds. No abnormal sounds were noted on auscultation of the lungs. He was in good body condition with a body condition score of 5/9, and he weighed 65 kg. He was normothermic with a temperature of 102.5*F, and he was panting. He was non-ambulatory paraparetic with minimal motor function in his hind limbs. His cranial nerve tests were within normal limits, and proprioception was absent in his hind limbs. His segmental reflexes were intact and normal in all four limbs, and his cutaneous trunci reflex was within normal limits as well. Pain was elicited on palpation of the thoracic vertebrae around the fifth thoracic vertebrae. His lesion was localized to T3-L3 based on his neurologic exam.

Diagnostic Approach and Treatment:

Thoracic radiographs were taken to further evaluate the thoracic spinal mass palpated and the holosystolic heart murmur. A bulge was noted at the region of the main pulmonary artery, but obliquity of the cardiac silhouette was considered for this abnormality. Lesser consideration was given to pulmonic stenosis. Thoracic radiographs also revealed permeative lysis of the fifth thoracic spinous process with a faint remnant of the cranial border. There was also irregular,

periosteal proliferation along the caudal aspect of the fourth and sixth spinous processes and the cranial aspect of the seventh spinous process. Computed tomography with contrast of the spine was then performed to further evaluate this area and revealed a soft tissue attenuating, contrast enhancing mass causing expansion and near complete destruction of the fifth thoracic spinous process and dorsal laminae. This mass also expanded into the adjacent epaxial musculature and into the spinal canal at the level of the fifth thoracic vertebrae. The mass was extending from the fourth thoracic spinous process though the seventh. A urinalysis and urine culture were also submitted at this time due to Maverick's history of possible urinary issues. His urinalysis revealed trace protein, a moderate amount of blood with 10-25 red blood cells and 5-10 white blood cells. No growth was seen after 48 hours on the urine culture.

Due to the aggressiveness of the lesion seen on radiographs and CT, the poor prognosis of Maverick's condition was discussed with the owners at this time. Despite the poor prognosis, his owners elected to send Maverick to surgery to decompress the spinal cord and to remove as much of the mass as possible. Due to the likelihood of neoplasia, abdominal radiographs and ultrasound were performed to check for signs of metastasis before surgery. No signs of metastasis were noted at this time, and Maverick was taken to surgery the evening of 6/28/19. During surgery, a pocket of purulent material was found dorsal to T5 and two samples were taken for culture. The tumor was found to be quite vascular during the surgery and a whole blood transfusion of 400 ml was given to Maverick during surgery due to significant blood loss. The tumor was noted to invade the spinal canal during surgery, and as much of the tumor was removed as possible. The spinal cord was well decompressed during the surgery, and a fat graft was placed over the exposed spinal canal. Multiple areas of the mass were saved in formalin during surgery and submitted for biopsy.

Maverick was maintained on a fentanyl continuous rate infusion (CRI) during surgery set at 2.5 mcg/kg/hr that was continued until the evening of 6/29/19. He was also kept on maintenance Lactated Ringer's fluids set at 160 ml/hr that was discontinued on 6/30/19. An indwelling urinary catheter was placed before surgery, and his urine output was monitored closely and measured every 4 hours. His urine output ranged from 0.65 – 2.4 ml/kg/hr overnight after his surgery, and his urinary catheter was pulled the morning of 6/30/19. Maverick was also started on pantoprazole at 1 mg/kg intravenously every 12 hours, gabapentin at 9 mg/kg orally every 8 hours, diazepam at 0.2 mg/kg orally every 8 hours, maropitant at 1 mg/kg intravenously every 24 hours, trazadone at 3 mg/kg orally as needed for anxiety while in the intensive care unit. After discontinuing the fentanyl CRI, Maverick was switched to Tylenol 4 at 2 mg/kg orally every 8 hours for pain management.

No aerobic or anaerobic growth were seen on culture of the purulent material after 48 hours. Biopsy of the mass revealed a densely cellular, unencapsulated mesenchymal neoplasm with frequent and bizarre mitotic figures present. Mitotic rates were high (about 24 per high powered fields), and moderate anisocytosis and anisokaryosis with frequent binucleate and rare trinucleate cells were present. Large areas of hemorrhage and necrosis were also noted throughout the mass. The mass stained strongly for S100 and vimentin, variably for smooth muscle actin and negatively for cytokeratin, desmin, GFAP, MUM1 and CD18. Positive vimentin staining confirmed mesenchymal origin of the tumor[6]. The definitive cell origin of the mass could not be discerned, but it was most consistent with an anaplastic sarcoma of muscle origin based on special staining. The tumor was determined to be highly malignant and a grave prognosis was given by the pathologists.

Pathophysiology:

Soft tissue sarcomas are tumors that arise from mesenchymal cell origin and comprise approximately 15% of all skin and subcutaneous tumors in dogs[1]. These sarcomas are further classified by histologic appearance and named after the connective tissue that they arise from. They tend to occur in middle-aged to older dogs and often present as firm, fixed masses involving the extremities, oral cavity and trunk of the animal[1]. The metastatic potential for soft tissue sarcomas is poorly described with reported rates ranging from 1.7 to 41%, but the metastatic potential is likely associated with a higher histologic grade and mitotic count[2]. Common histologic features of soft tissue sarcomas include an ability to arise from any anatomical site in the body, they often appear as pseudo encapsulated with poorly defined margins, have a tendency to infiltrate fascial planes, commonly recur locally after conservative surgical excision, often metastasize through a hematogenous route, and poor response to chemotherapy and radiation is often seen when a gross tumor is present[3]. The cause of sarcoma oncogenesis is unknown in most cases, but parasitic infections such as *Spirocerca lupi*, trauma and implants have been reported to lead to sarcoma development[2].

When the tissue of origin cannot be determined, they are classified as anaplastic or undifferentiated sarcomas. Anaplastic cells are poorly differentiated or undifferentiated and often show advanced pleomorphism. Anaplastic tumors often have high mitotic activity, lack of normal structure and loss of cell orientation[7]. These bizarre features and the ability of these anaplastic cells to up or down regulate their expression of different genes can make them difficult to identify on histopathology even with advanced staining. Anaplastic sarcomas are rare in dogs, accounting for less than 0.5% of cutaneous neoplasms. Additionally, the average age of onset in dogs is eight years, and they tend to be highly aggressive tumors[5]. In 2016, researchers

revised a cohort study from 1998 to 2004 of proliferative lesions from a study in Golden Retrievers that had been determined to be unclassified soft tissue sarcomas. They used newer immunohistochemistry (IHC) methods to try and further identify these sarcomas to determine the tissue of origin. After the study, 17 out of the 110 samples remained unclassified sarcomas[4]. The study stated that these 17 tumors were poorly differentiated and likely lacked the lineage markers used in the IHC methods.

Regardless of the originating tissue, wide surgical excision is the cornerstone of therapy for these sarcomas, but multimodal treatment is often used. Advanced imaging such as computed tomography is recommended for surgical planning to further evaluate the invasiveness of the tumor. If the tumors are amenable to wide surgical excision, surgical resection alone may be used if clean margins are achieved. Radiation is generally used when surgical excision is not possible or if clean margins are not achieved. Chemotherapy is often recommended for high grade sarcomas due to their likelihood of metastasis or in patients where metastasis has already been noted[8].

Case Outcome:

The day after his surgery, Maverick was taken on short, assisted walks starting that afternoon. Slight motor function was noted in his hind limbs at this time. Care was taken to turn him every 6 hours as well to help avoid pressure sores from developing. On 7/1/19, Maverick began putting weight on his back limbs with sling assistance during his walks and began eating and drinking normally. By 7/2/19, he was able to ambulate on his hind limbs with sling assistance. He was discharged on 7/3/19 and was sent home with a Help ‘Em Up Harness. At this time, Maverick was ambulating with minimal assistance and was squatting to urinate. He was sent home on Tylenol 4, gabapentin and diazepam with instructions for him to be strictly rested

for the next 2 weeks until his re-check appointment. Due to the aggressiveness of the tumor and invasion into the bone, the high risk of a pathologic fracture was discussed with the owners. Radiation therapy was also discussed with the owners as a possible addition to the surgical therapy at this time. His owners were going to consider this and let us know at a later time if they chose to pursue this option. They were instructed to monitor Maverick closely for any acute changes in his condition as this may indicate that a pathologic fracture has occurred which is a surgical emergency.

Unfortunately, Maverick's owners called on 7/8/19 to let us know that he was much more painful and was not putting weight on his hind limbs anymore. He presented the next day and was humanely euthanized at this time due to the high likelihood of a pathologic fracture of his vertebrae and subsequent damage to his spinal cord.

Conclusion:

It is important to note that Maverick's case was a rare one that strayed from the most common presentation of this disease. With Maverick's signalment and the bony involvement of the tumor, osteosarcoma was most likely. The p53 gene encodes a nuclear phosphoprotein that is a tumor-suppressor gene. Great Danes have been shown to have a higher p53 index, making them more susceptible to osteosarcomas[9]. The incidence of osteosarcoma in dogs has an early peak at 18-24 months of age in addition to its later peak age of onset[10]. While they mostly affect the appendicular skeleton, they have been documented in the axial skeleton as well[11].

However, Maverick's case does exemplify the aggressive nature that canine soft tissue sarcomas can possess. Even if the tumor does not metastasize, it can cause pathology by invading into neighboring tissues. For example, the invasion of Maverick's tumor into his spinal canal caused compression of his spinal cord, leading to his presenting clinical signs. Invasion of

the tumor into bony structures can weaken the bone as well, leading to pathologic fractures. Clinical signs associated with soft tissue sarcomas can vary greatly depending on the location of the tumor, invasiveness into surrounding structures and size of the tumor. The tissue of origin of Maverick's tumor could not be determined due to the nature of anaplastic cells. These neoplastic cells can down regulate genes that code for the specific substances that are stained for. These cells often do not resemble normal cells from the originating tissues, making it more difficult to identify them.

Ultimately, the local invasiveness of Maverick's sarcoma led to his demise. While complete surgical excision of the tumor could not be obtained, decompression of the spinal cord during surgery allowed Maverick to walk again after surgery. Although a necropsy was not done to confirm, a pathologic fracture of his thoracic vertebrae due to weakening of these bones by the neoplastic process likely occurred.

Resources:

1. Ehrhart, N. (2005). Soft-Tissue Sarcomas in Dogs: A Review. *Journal of the American Animal Hospital Association*, *41*(4), 241–246. doi: 10.5326/0410241
2. Bray, J. P. (2016). Soft tissue sarcoma in the dog - part 1: a current review. *Journal of Small Animal Practice*, *57*(10), 510–519. doi: 10.1111/jsap.12556
3. Withrow, S. J. (2013). *Withrow et MacEwens small animal clinical oncology*. St. Louis, MO: Elsevier.
4. Boerkamp, K. M., Hellmén, E., Willén, H., Grinwis, G. C. M., Teske, E., & Rutteman, G. R. (2016). Unclassified sarcomas. *Journal of Veterinary Diagnostic Investigation*, *28*(6), 623–631. doi: 10.1177/1040638716660130
5. Gross, T.L., Ihrke, P.J., Walder, E.J. & Affolter, V.K. (2005) Skin Diseases of the Dog and Cat. Clinical and Histopathologic Diagnosis. Oxford, UK: Blackwell Publishing.
6. Pernick N. Vimentin. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/stainsvimentin.html. Accessed February 8th, 2020.
7. Haschek, W. M., Rousseaux, C. G., & Wallig, M. A. (2010). *Fundamentals of toxicologic pathology*. Amsterdam: Boston.
8. Nicole Ehrhart (*2005*) Soft-Tissue Sarcomas in Dogs: A Review. *Journal of the American Animal Hospital Association*: July/August 2005, Vol. 41, No. 4, pp. 241-246. https://doi.org/10.5326/0410241
9. Loukopoulos, P., Thornton, J. R., & Robinson, W. F. (2003). Clinical and Pathologic Relevance of p53 Index in Canine Osseous Tumors. *Veterinary Pathology*, *40*(3), 237–248. doi: 10.1354/vp.40-3-237

10. Ehrhart, Nicole. (July 2014). Canine Osteosarcoma: Part 1. Clinician's Brief. https://files.brief.vet/migration/article/19076/canine-osteosarcoma-part-1-19076-article.pdf
11. Dickerson, M. E., Page, R. L., Ladue, T. A., Hauck, M. L., Thrall, D. E., Stebbins, M. E., & Price, G. S. (2001). Retrospective Analysis of Axial Skeleton Osteosarcoma in 22 Large-Breed Dogs. *Journal of Veterinary Internal Medicine*, *15*(2), 120–124. doi: 10.1111/j.1939-1676.2001.tb01242.x
12. Mayer, M.N. and LaRue, S.M. (2005). Soft Tissue Sarcomas in Dogs. *Canadian Veterinary Journal.* Vol. 46, pp 1048-1052.