The Fall of Argos

A Case of Splenic Hemangiosarcoma

Anne Elise Hertl

Mississippi State University

College of Veterinary Medicine

Class of 2020

Clinicopathological Conference

January 10, 2020

Advisor: Brittany Baughman, DVM, M.S., Dipl. A.C.V.P.

Co-Advisor: Nataly Mamaliger, DVM

INTRODUCTION:

Hemangiosarcoma (HSA) is a mesenchymal neoplasm that is of malignant endothelial origin. It is more commonly found in dogs than cats. Large breed dogs are primarily affected such as German Shepherds, Golden Retrievers and Labrador Retrievers. Middle aged to older dogs and cats are primarily affected. The three most common locations of hemangiosarcomas are cutaneous, subcutaneous and visceral. Cutaneous hemangiosarcoma is commonly associated with UV exposure and often has a low metastatic rate. Subcutaneous hemangiosarcoma is not associated with UV exposure and relatively has a high metastatic rate. Visceral hemangiosarcomas are generally highly malignant and metastatically aggressive. The risk factors associated with visceral hemangiosarcoma are unknown, but they are suspected to be multifactorial including radiation exposure for example.[7,8] The three most commonly reported primary tumor sites are the spleen, right atrium and skin.[8]

Presentation of HSA can vary depending on its location. Dogs with cutaneous HSA can be asymptomatic or present with ulceration or bleeding. Abdominal HSA can present with hemoabdomen, pale mucous membranes, poor femoral pulses, acutely weak, and sudden death. Dogs with right atrium HSA may exhibit lethargy, dyspnea, have a distended abdomen, pericardial effusion, right sided heart failure, and may only present dead.[8]

HISTORY AND PRESENTATION:

Argos is a 7-year-old intact male Belgian Malinois and worked for the sheriff's department tracking down fugitives and finding illegal narcotics. On August 29, 2019, Argos presented to his referring DVM for being acutely down in the rear. On physical exam, he was not painful, but he did have mild ataxia and conscious proprioceptive deficits in both hindlimbs.

He was prescribed Sucralfate, Methocarbamol, and he received a Torbutrol injection. He also received Dexamethasone SP injections on the 29th and 30th. On September 4, 2019, Argos presented to his referring DVM for intermittent right forelimb lameness. He was still ataxic and had conscious proprioceptive deficits in both hindlimbs. He was prescribed Prednisone 20 mg. On September 16, 2019, he presented to his referring DVM for diarrhea. He had conscious proprioceptive deficits, moderate ataxia and a hypermetric gait in both hindlimbs. He was able to walk well, and he was improving. He was given Metronidazole and Sucralfate for the diarrhea. On September 20, 2019, he was ataxic in all four limbs, and he was crossing his forelimbs and hindlimbs. Argos presented to MSU-CVM VSC on September 20, 2019 for suspected intervertebral disk herniation.

Upon presentation to MSU-CVM VSC, Argos had a temperature of 101.9 F, a pulse of 120 beats/minute, a respiration of 28 breaths/minute, and pale mucous membranes. He weighed 26 kg with a BCS of 5/9. On cardiothoracic auscultation, no murmurs, arrhythmias, crackles or wheezes were appreciated. His neurologic exam revealed a normal mental status, and he was classified as non-ambulatory tetraparetic. He had deep pain sensation in his forelimbs and hindlimbs. His cranial nerves, cutaneous trunci and muscle tone were all normal. All segmental reflexes were normal except for a decreased flexor withdrawal in the right front forelimb. There was no hyperpathia noted. His neuroanatomical localization was in the cervical to cervical-thoracic spinal cord.

DIAGNOSTICS:

A CBC, neuro chem panel, coagulation profile, occult heartworm 4dx were run. His CBC consisted of decreased RBC, Hgb, Hct, MCV, MCHC, platelets, PCV and elevated

segmented neutrophils. His RBC morphology revealed polychromasia of red blood cells indicating a regenerative response, however an absolute reticulocyte count was not performed for confirmation. The neuro chem panel revealed slightly decreased sodium, carbon dioxide, and magnesium. It also revealed slightly elevated BUN and phosphorus. There were no abnormalities found in Argos' coagulation profile and the occult heartworm 4dx test was negative.

An AFAST scan was performed in the ICU, where a large bladder was visualized. There was no free fluid found on ultrasound. A red rubber catheter was placed to relieve his bladder and 420 mls of urine was expelled. Next, abdominal and thoracic radiographs were performed. Abdominal radiographs revealed that the colon was deviated ventrally at L7, a soft tissue structure ventral to L7, and a round mass protruding from the spleen. Chest radiographs showed a diffusely structured interstitial pulmonary pattern found throughout all lung lobes. These radiographic findings were most consistent with metastatic neoplasia. Due to Argos' poor prognosis, he was humanely euthanized and submitted for necropsy.

NECROPSY & MICROSCOPIC FINDINGS:

Gross necropsy findings included multifocal, raised, tan to red nodules in the spleen, and the largest splenic mass was measured at 5 x 7 x 4 cm. On cut surface, these nodules were filled with blood caverns. Also, the spleen was contracted. The serosal surfaces of the intestines and stomach had similar small, dark red nodules. The multifocal nodules found on the intestines and stomach were transmural. Small, dark red nodules were also appreciated in the right and left renal cortices. There were widely disseminated dark red, raised nodules (0.5 x 0.5 cm) scattered throughout the parenchyma of all lung lobes and the endocardium of the right auricle. There was

a raised, oval mass (3 x 4 x 1 cm) on the ventral aspect of the fifth cervical vertebra, which only involved the bone. The vertebral body of C5 was porous, roughened, easily broken and black indicating bony lysis. There were small, irregular extradural masses at L1 and L2, which were compressing the spinal cord.

On histopathology, the largest splenic mass was composed of biphasic neoplastic cells. The neoplastic cells were predominantly polygonal shaped with distinct cell borders, abundant eosinophilic cytoplasm, large irregularly shaped nuclei with finely stippled chromatin and one to two prominent nucleoli. There were also many red blood cells interspersed with the polygonal cells. Within some areas of the mass, there were spindleoid neoplastic cells. These spindleoid neoplastic cells were wrapped around bundles of collagen forming irregular vascular channels. There were around 32 mitoses per 10 high powered fields, and there was significant anisocytosis and anisokaryosis. There were many areas of necrosis throughout the splenic mass. The metastatic lesions had similar histopathologic features to the splenic mass. Histopathologic findings of the extradural mass found in the L1-L2 spinal cord included severe vacuolation of the white matter tracts of the dorsal and ventral funiculi. The white matter tracts of the dorsal and ventral funiculi often contained eosinophilic material and occasional Gitter cells. There was vacuolation of the axonal sheaths, and they were composed of eosinophilic material and Gitter cells.

PATHOPHYSIOLOGY:

Hemangiosarcoma has been historically known as a mesenchymal neoplasm arising from malignant endothelial cells. Any vascular structure within body tissues and organs can be affected by HSA. The 3 most common reported sites for primary HSA to occur are the spleen,

right atrium and skin. HSA can be insidious due to the growth rate being relatively slow, but this is not always the case. Some dogs may not show clinical signs, while other dogs may die suddenly. HSA invades normal tissues that surround the primary tumor and have the potential to metastasize to distant tissues or organs. Blood vessels that are associated with tumors are often convoluted and distorted allowing blood to pool and predisposing to clot formation and infarction. This may result in variably sized ruptures in the tumor. Blood can escape through these ruptures and can cause hemorrhage within the abdomen, subcutaneous space, pericardial sac or pleural cavity.[7]

The etiology of hemangiosarcoma development is not completely understood. However, breed predilection is a consistent finding in HSA, such as the German Shepherd. This suggests that heritable traits contribute to HSA, but it is not the single factor. Environmental factors, ionizing radiation exposure and infectious diseases can be risk factors for developing HSA. Historically, it was presumed that HSAs arose from malignant endothelial cells due to their histological appearance. Recent data suggests that the cellular origin of HSA is derived from hematopoietic progenitor cells in the bone marrow. The hematopoietic progenitor cells in the bone marrow are transformed into hemangiosarcoma cells by chromosome translocations and a reactive microenvironment. These hemangiosarcoma cells then produce IL-8. IL-8 is a pro-inflammatory cytokine that is thought to control the tumor microenvironment by promoting the tumor cells' growth and survival. The hemangiosarcoma tissue is rich in CXCR4 (chemokine receptor type 4) and its ligand, CXCL12. CXCR4 and its ligand, CXCL12, are responsible for increasing tumor cells' motility for migration and invasion to other locations for metastasis. Finally, some of the hemangiosarcoma cells consume Sphingosine-1-phosphate (S1P). By consuming S1P, this increases tumor cell growth and survival.[7]

TREATMENT:

The traditional treatment of choice for splenic hemangiosarcoma has been splenectomy when there is one nodule and no sign of metastasis.[3] The median survival time (MST) of a splenectomy alone is 1-3 months. The addition of doxorubicin based chemotherapy along with splenectomy has increased MST to 5-6 months.[2,3,4,8] Doxorubicin based chemotherapy can include Doxorubicin, Doxorubicin and Cyclophosphamide or Doxorubicin/Vincristine/Cyclophosphamide.[4] Toceranib has been used in clinical trials for dogs who had stage I and stage II HSA. There were 31 dogs who had a splenectomy, received doxorubicin 2 weeks afterwards, and then received toceranib. The 31 dogs MST was 172 days.[4] Another study consisted of 21 dogs that were treated with deracoxib and doxorubicin after a splenectomy. The overall median survival time for dogs with Stage I, II and III hemangiosarcoma was 150 days. However, dogs with Stage III HSAs had a higher MST than dogs with Stage II HSAs.[6] There have been other treatments used to treat HSA at different stages of the metastatic cascade including integrin mediated therapy, minocycline, interferon, thalidomide, endostatin, matrix metalloproteinase inhibitors, inhalation chemotherapy, biologic response modifiers, and dietary modification. These treatments made no significant improvements with MST of dogs with HSA.[3]

Although hemangiosarcomas can be staged, staging was based from the cutaneous form, and it does not translate well for visceral HSAs.[2,8] HSAs can be staged by using different diagnostics. These diagnostics include CBC, chemistry profile, coagulation profile, thoracic and abdominal radiographs, echocardiogram and ultrasound. Biopsy is the gold standard for diagnosing HSA.[8] Earlier stages of HSA have increased MST when being treated in comparison to later stages. There is a clinical staging system used to stage visceral hemangiosarcomas in one

of the clinical trials, and it is based from the World Health Organization scheme. In Stage I, there is no evidence of a tumor or it is confined to the primary organ. In Stage II, the tumor has metastasized to the regional lymph nodes. In Stage III, the tumor has metastasized to the distant lymph nodes.[2]

CONCLUSION:

Hemangiosarcomas are the most common metastatic neoplasia to the dogs' central nervous system mainly involving the cerebrum. Gray matter is usually affected as opposed to white matter, most likely due to their differences in vascularity and blood flow.[9] In cases where hemangiosarcoma metastasizes to the CNS, dogs can have neurological signs like Argos did. The extradural masses in the lumbar region that compressed the spinal cord were causing paresis in both hindlimbs. The lumbar mass most likely came first, then the cervical vertebral mass. Argos' forelimb neurological signs are attributed to the bony lysis found in the vertebral body of C5 causing him instability and paresis of both forelimbs. The largest mass which was found in the spleen was most likely the primary site of Argos' hemangiosarcoma.[9] Argos' splenic hemangiosarcoma metastasized to multiple organs including his stomach, intestines, kidneys, lumbar spine, C5 vertebra, heart, lung and skin. His previous onset of diarrhea may have been due to the lesions found in his stomach and intestines, but it may be attributed to taking steroids.

Splenic hemangiosarcomas still carry a grave prognosis regardless of the treatment protocol. Chemotherapy along with splenectomy have slightly improved MST from 1-3 months to 3-6 months. Even with treatment, due to the hemangiosarcoma's metastatic nature, the dogs don't usually survive past a year.[3,4] The best way to improve MST of a dog with hemangiosarcoma is to detect it early.[3] Argos' MST could have potentially increased with early

detection, but he would still have a guarded prognosis. In Argos' case, it is a reminder to us all that a good physical exam including looking at mucous membranes can be the key to helping us diagnose a patient with hemangiosarcoma.

References

1. Aschenbroich, S., Woolcock, A., & Rissi, D. R. (2014). Paraparesis in a Golden Retriever. *Veterinary Pathology*, *51*(5), 996–999.
2. Batschinski K, Nobre A, Vargas-Mendez E, et al. Canine visceral hemangiosarcoma treated with surgery alone or surgery and doxorubicin: 37 cases (2005-2014). *Can Vet J*. 2018;59(9):967–972.
3. Clifford CA, Mackin AJ, Henry CJ. Treatment of Canine Hemangiosarcoma: 2000 and Beyond. JOURNAL OF VETERINARY INTERNAL MEDICINE. 2000;(5):479.
4. Gardner HL, London CA, Portela RA, et al. Maintenance therapy with toceranib following doxorubicin-based chemotherapy for canine splenic hemangiosarcoma. *BMC Vet Res*. 2015;11:131. Published 2015 Jun 11.
5. Herman, E. J., Stern, A. W., Fox, R. J., & Dark, M. J. (2019). Understanding the Efficiency of Splenic Hemangiosarcoma Diagnosis Using Monte Carlo Simulations. *Veterinary Pathology*, *56*(6), 856–859.
6. Kahn SA, Mullin CM, de Lorimier LP, et al. Doxorubicin and deracoxib adjuvant therapy for canine splenic hemangiosarcoma: a pilot study. *Can Vet J*. 2013;54(3):237–242.
7. Kim J-H, Graef AJ, Dickerson EB, Modiano JF. Pathobiology of Hemangiosarcoma in Dogs: Research Advances and Future Perspectives. Veterinary Sciences. 2015; 2(4):388-405.
8. Thomason, J. (2018). Sarcomas II Lecture. Small Animal Medicine and Surgery
9. Meuten, Donald J. Ed. *Tumors in Domestic Animals 4th edition*. Iowa State Press, 2002.