

Bella's Big Belly

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Class of 2022

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**Introduction:**

Hemangiosarcoma is a commonly occurring vascular neoplasia that is highly invasive with a high rate of metastasis to other organs. Hemangiosarcoma is often seen older dogs, with the median age of 9-12 years old. This neoplasia can be found in nearly all dog breeds but is commonly found in German Shepherds, Golden Retrievers, and Labrador Retrievers. There is no definite sex predilection, but there is suspicion that there is an increased prevalence in males<sup>2</sup>. Hemangiosarcoma is commonly found in the spleen 28-50% of the time, right atrium and auricle 3-50% of the time, and the skin in 13% of cases<sup>2</sup>. This neoplasia readily metastasizes hematogenously most commonly to the liver, lungs and omentum<sup>4</sup>. The exact etiology is unknown, but an inherited or familial predisposition is suspected due to the strong breed association observed.

Staging of hemangiosarcoma can provide indication on the likely survival time for the patient. Dogs that are stage 1 have no hemoabdomen and no clinically detectable metastases. Those with stage 2 have a hemoabdomen, but no clinically detectable metastases and are considered stage 3 when there are clinically detectable metastases<sup>1</sup>. Understanding the patient's stage is essential when it comes time to communicate to clients about long term goals and prognosis.

**History and Presentation:**

Bella, a 9-year-old female spayed Golden Retriever, presented to MSU-CVM's Small Animal Emergency Service on 4/21/21 for a suspected bleeding abdominal mass. On Monday, April 12<sup>th</sup>, Bella presented to her primary veterinarian for consultation for a dental. Pre-anesthetic blood work was performed and revealed a thrombocytopenia. The dental was not performed, and bloodwork was repeated a couple of days later. Her second blood panel revealed

a persistent thrombocytopenia, and a blood panel was submitted for a Coomb's test. Bella was prescribed prednisone (30 mg BID) for presumptive immune mediated thrombocytopenia. Bella presented to her primary veterinarian on 4/21 for radiographs and an abdominal ultrasound. The ultrasound revealed free fluid in the abdomen, along with a mass with the suspect origin being the spleen. Due to the concern for a possible hemoabdomen, Bella was referred to MSU-CVM for further diagnostics and care.

On presentation, Bella was bright, alert, and responsive. She had a BCS of 6/9. Her TPR was within normal limits, and she had a CRT of less than 2 seconds with pale pink and moist mucous membranes. Her ECG was normal with no arrhythmias observed and was oxygenating normally. Her TFAST showed no free fluid, but her AFAST showed free fluid at the cystocolic and diaphragmatic hepatic junctions.

Bella presented with a slightly abnormal presentation. Typical presentation for hemangiosarcoma is a dog in sudden hemodynamic collapse due to nontraumatic organ rupture. These patients present with weakness, collapse, pale mucous membranes, tachycardic, cardiac arrhythmias and poor pulse quality<sup>3</sup>. Since Bella appeared to be stable and her blood work abnormalities were found on routine bloodwork, she has the more atypical presentation of nonspecific lethargy and likely intermittent hypovolemia.

### **Pathophysiology:**

The etiology and cellular origins of hemangiosarcoma are not well understood. It is known that the spleen is the most common location for this neoplasia and its dysfunction is the cause of the classic signs of a ruptured hemangiosarcoma. The spleen is an interesting organ because it has an immunologic and hematologic role in the body<sup>5</sup>. One of the primary roles of the spleen is to filter blood, while at the same time, the spleen is surveying for blood borne

pathogens and destroying old red blood cells. The spleen contains both a white pulp and a red pulp with a capsule on the outside. The white pulp contains lymphoid tissue and is where B and T cells are produced. The red pulp can also undergo extramedullary hematopoiesis when needed and contains venous sinuses that can hold up to 30% of the animal's blood volume at one time. On average, the entire blood volume will be filtered through the spleen once daily. The large blood-holding capacity of the spleen is the reason hemangiosarcoma tumors can be so devastating when they rupture causing a significant hemoperitoneum, often resulting in hypovolemic shock.

There are three phases of hypovolemic shock, early/compensated, early decompensated and terminal. The very early stages of hypovolemic shock are often missed. Catecholamines are released in response to the decreased blood volume resulting in increased cardiac output<sup>8</sup>. This stage can be recognized clinically as increased heart rate, bounding pulses and a rapid capillary refill time<sup>8</sup>. As the blood volume continues to leak into the abdomen there will be less blood flowing to organs like the kidneys resulting the second phase which will result in lactic acidosis due to tissue hypoxia. The anaerobic metabolism results in metabolic acidosis which leads to cellular destruction that can result in acute respiratory distress syndrome and multiorgan dysfunction syndrome<sup>8</sup>. The final stage of shock will no longer be responsive to fluid therapy. Once the final stage of shock occurs, the compensatory mechanisms have failed, and the heart and brain begin to experience tissue hypoxia. The reduced blood flow to the brain eventually decreases the respiratory and sympathetic neural centers<sup>8</sup>. When this happens the heart rate will slow, vessels will vasodilate, and blood will begin to pool. The patient will have severe hypotension, bradycardia, pale or cyanotic mucus membranes, weak pulses and often appear in a comatose state<sup>8</sup>. Patients are commonly brought into the clinic when they are in the second stage

of hypovolemic shock and can be stabilized with fluids and blood transfusions before being brought to surgery for their hemoabdomen.

**Diagnostic approach/considerations:**

Hemangiosarcoma has a characteristic presentation: an old, large-breed dog that suddenly collapses or presents with fluid-filled abdomen. This can lead clinicians to make presumptive diagnosis of hemangiosarcoma. In order to definitively diagnose a tumor type, it is essential to obtain histopathology. Cytology of fine needle aspirates are often unsuccessful due to the highly vascular nature of the tumor that results in high blood contamination.

When a dog presents it is important to do some baseline diagnostics to determine the overall health of the dog. A complete blood count often reveals evidence of regenerative anemia, anisocytosis, polychromasia, thrombocytopenia and reticulocytosis. Nearly 50% of the dogs that present for hemangiosarcoma also have acanthocytosis. Schistocytes and elevated number of nucleated RBC are present due to the abnormal spleen or due to hypoxemia, bone marrow infiltration, and extramedullary hematopoiesis<sup>4</sup>. Serum chemistries are often nonspecific but can reflect organ system involvement like liver infiltration reflected in increased liver enzymes<sup>4</sup>. Coagulation profiles can reflect disseminated intravascular coagulopathies with increased PT and PTT.

In order to stage hemangiosarcoma and help clients make an educated decision on how they would like to proceed after the presumptive diagnosis is made, it is important to perform an abdominal ultrasound, abdominal radiographs and 3-view chest radiographs. Abdominal ultrasound may show a highly vascular mass which is often of splenic origin. The ultrasound can also indicate if there are any other masses within the abdomen. Abdominal radiographs will often show splenomegaly, hepatomegaly, intra-abdominal masses and loss of detail suggestive of

hemoperitoneum<sup>4</sup>. Thoracic radiographs are needed to look for pulmonary or thoracic metastasis<sup>5</sup>. Radiographs may also show globoid cardiac appearance due to pericardial effusion or due to a soft tissue heart base mass<sup>4</sup>. Metastasis and hemoabdomen are poor prognostic indicators that need to be addressed. It is important to remember that definitive diagnosis of hemangiosarcoma can only be made with histopathology and diagnostic imaging or even visual appearance is not enough to differentiate between splenic masses.

### **Treatment and Management options:**

In most cases the primary goal when a dog presents in hemodynamic shock with a hemoabdomen is stabilization by performing a palliative splenectomy with liver biopsies<sup>1</sup>. Even though the splenectomy stops the most immediate problem, the median survival time of patients after surgery is 1.5-3 months<sup>1</sup>. Surgical excision alone has not shown to extend survival even if the surgery is performed because the mass was found a routine physical exam. There are a variety of chemotherapy protocols available that can slightly extend the survival time; however, there has been no evidence of one superior protocol<sup>1</sup>. One of the mainstays of adjunctive therapy is the chemotherapeutic agent, doxorubicin, which works by inhibiting DNA synthesis, DNA-dependent RNA synthesis and protein synthesis with tumor cells. There are three common chemotherapeutic protocols all involving doxorubicin. The first being doxorubicin alone IV every 3 weeks for up to 5 cycles. The second is doxorubicin and cyclophosphamide; doxorubicin is the same as the first protocol with cyclophosphamide added IV on days 3-6 of every 3-week cycle. The last protocol is doxorubicin as the same as the first two in 3-week cycles with cyclophosphamide incorporated in IV on day 1 of every 3-week cycle, and vincristine added IV on days 8 and 15 of each cycle<sup>2</sup>. Interestingly, the method of delivery of the chemotherapeutic agent may play a role in better slowing the rate of metastasis depending on location<sup>2</sup>. This means

that using inhaled doxorubicin for pulmonary metastasis instead of IV has shown to delay the rate metastasis in recent studies<sup>2</sup>. Doxorubicin has also been used in pegylated liposomal encapsulated cells which has been shown to prolong the drug delivery and therefore the overall tumor exposure to the drug<sup>2</sup>. Research is being done on intracavitary administration of cisplatin or carboplatin for abdominal metastasis and has shown success with abdominal metastasis<sup>2</sup>. Even with chemotherapy and surgical resection of the mass, the median survival time is often only 3-6 months<sup>1</sup>. Clients should be well educated about the poor prognosis associated with hemangiosarcoma and, even if they pursue all treatments possible, their pet will likely not survive more than a year after diagnosis.

Diet is an important aspect of any patient with neoplasia. The Neoplastic Diet, by Hills, is designed to combat cancer cachexia, weight loss despite adequate nutritional intake. This diet is low in simple carbohydrates, has a moderate amount of highly bioavailable protein, is high in omega 3 fatty acids, and contains amino acids like arginine, glycine, glutamine and cysteine<sup>2</sup>. Fat is the major energy source in the diet because tumor cells are not able to use fat as an energy source and thus slow growth<sup>2</sup>. The omega 3 fatty acids have been shown to have antiangiogenic properties and may help inhibit tumor development<sup>2</sup>. However, if this diet is not palatable to the specific patient, then a normal diet should be given. It is imperative that the dog continues to eat.

As a last-ditch option as medical management or postoperative care Yunnan baiyao has been used for its potential procoagulant properties<sup>3</sup>. Yunnan baiyao, a Chinese herbal supplement, is believed to be an immunostimulant and have the potential in delaying abdominal metastases. The role and understanding of the supplement is not completely understood and there has been little research into the validity of its claims.

## Case Outcome:

Prior to surgery, MSU-CVM's Emergency department performed a complete blood count, chemistry panel and coagulation profile. The CBC revealed leukophilia ( $26.81 \times 10^3/\text{ul}$  with reference range of  $5-14.20 \times 10^3/\text{ul}$ ), anemia ( $3.85 \times 10^6/\text{ul}$  with reference range of  $5.60-7.60 \times 10^6/\text{ul}$ ), thrombocytopenia ( $40 \times 10^3/\text{ul}$  with reference range of  $156-455 \times 10^3/\text{ul}$ ), neutrophilia ( $23056.6 /\text{ul}$  with reference range of  $31000-11800 /\text{ul}$ ) with bands ( $536 /\text{ul}$  with reference range of  $0-400 /\text{ul}$ ), and nucleated RBCs ( $3/100 \text{ WBC}$ ). Occasional polychromasia, poikicytosis, echinocytes, hypochromia and rare Howell jolly bodies were observed on the blood smear. The chemistry revealed elevated ALT ( $92 \text{ U/L}$  with reference range of  $10-90 \text{ U/L}$ ), ALP ( $372 \text{ U/L}$  with reference range of  $11-140 \text{ U/L}$ ) and total bilirubin ( $0.7 \text{ mg/dl}$  with reference range of  $0.2-0.6 \text{ mg/dl}$ ). The coagulation profile was within normal limits. Intra-operative, Bella, was blood typed and was DEA Negative.

On April 21<sup>st</sup>, 2021, Bella underwent a splenectomy with liver biopsy. She was anesthetized and positioned in dorsal recumbency. She was prepped and sterilely draped for surgery. A standard ventral abdominal midline approach was performed. Once the abdomen was open, the falciform ligament was excised using monopolar cautery. Approximately 1L of blood was present in the abdomen. A Poole suction tip was used to better visualize the surgical field. An abdominal explore of the cranial abdomen was done and was unremarkable. The spleen was noted to have a mass and large hematoma located at the tail end. The spleen was removed using a Ligasure that cut tissue and cauterized vessels at the same time. The liver was checked for nodules, but there were none palpable or visible. A punch biopsy was taken from a portion of the left liver lobe and was submitted for histopathology. A whole blood transfusion was given intra-operatively. The abdomen was lavage with approximately 4 L of warmed sterile saline, and the



abdominal wall was closed using 0 PDS in a simple continuous pattern. The subcutaneous tissue was closed using 3-0 Monocryl in a simple continuous pattern. The skin was then closed with wide skin Staples<sup>5</sup>.

Post-operatively Bella had continuous ECG and blood pressure checks throughout the next 24 hours. She maintained normal sinus rhythms the majority of the time but did have occasional PVCs. She remained on a fentanyl at 5 mcg/kg CRI for pain until 5pm on April 22<sup>nd</sup>, when she was then switched to oral Tylenol 4 at 2 mg/kg every 8 hours. Bella was maintained on maintenance plasmalyte throughout her entire ICU stay and would readily eat canned chicken when offered. Since she was eating and drinking on her own, she was moved to surgery wards on April 23<sup>rd</sup>.

Histopathologic results from the splenic biopsy confirmed hemangiosarcoma. The liver biopsy did not show any metastasis to her liver but did reveal a diffuse vacuolar hepatopathy. Bella's owners' main goal was to have more time with Bella and not have her in and out of the hospital. Because of this they did not elect further adjunctive therapy with MSU-CVM's Oncology Service.

Bella was discharged from MSU-CVM's Small Animal Surgery Service on April 23<sup>rd</sup>, 2021. She was sent home with Tylenol 4 at 2 mg/kg orally every 8 hours and instructions on post-operative care including E-collar, cold and warm packing, and exercise restrictions. Her owners were happy to bring her home and spend a few more comfortable months with her.

**Conclusion:**

The diagnosis of hemangiosarcoma is often a surprising and devastating disease for patients and their families. The abrupt decline in their previously healthy dog can be jarring for the families to understand, but as a veterinarian, it will be important to help educate your clients,

so they feel equipped in making the best decision for their family. Little is known about the etiology of this neoplasia and, despite knowing about hemangiosarcoma for decades, doctors have not been able to significantly extend the survival time. More research is currently being done that is looking at antimetastatic agents such as terferon and thalidomide that work to prevent angiogenesis<sup>2</sup>. Along with prevention of angiogenesis, researchers are looking into stopping the breakdown of the extracellular matrix with inhibitors like minocycline<sup>2</sup>. However, at this time, more research still needs to be done before they can be implemented into the treatment of hemangiosarcoma.

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