

**“Lady and the Tail”**

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## **Introduction:**

Hemangiosarcoma is a type of highly malignant neoplasia that arises from the vascular endothelium and can be further classified into two types: visceral and dermal variants.

Hemangiosarcoma most commonly occurs in dogs, with 5% of all non-cutaneous tumors and 12-21% of all mesenchymal tumors being hemangiosarcomas. It also represents 2.3-2.6% of skin tumors in dogs. It occurs far less commonly in the cat, encompassing only 0.5-2% of all neoplasms.<sup>15,19</sup> The visceral variant occurs more frequently in the dog. In contrast, the frequency of cutaneous and visceral locations for this neoplasm is evenly distributed between the two types in the cat.<sup>19</sup> Cutaneous hemangiosarcoma may occur as a primary neoplasm or in association with another site, such as the spleen or heart base.<sup>10</sup>

In dogs, there are several breeds that appear to be predisposed to development of hemangiosarcomas, most notably German Shepherds, Golden Retrievers, and Labrador Retrievers, though other large breeds are also commonly affected.<sup>15,19</sup> Dog breeds with very short hair, such as Whippets and Italian Greyhounds seem to be more predisposed to the dermal form.<sup>6,12</sup> There does not seem to be any breed predisposition in cats for development of hemangiosarcomas, though they are most commonly seen in domestic shorthair cats. Both cats and dogs that are lightly pigmented may be predisposed to development of the cutaneous form of the tumor in those areas.<sup>15,19</sup> The mean age of cats affected with cutaneous hemangiosarcoma is 11.5 to 12.5 years.<sup>20</sup> Some studies indicated that male cats were more predisposed, but others showed no sex predilection.<sup>9</sup>

Cutaneous hemangiosarcoma is staged based on the depth of the tumor.<sup>20</sup> A tumor associated only with the dermis is classified as stage 1. It becomes stage 2 when the tumor extends into the subcutaneous tissue, and when it is extending into the underlying musculature it

becomes stage 3. Dermal hemangiosarcomas that are stage 2 and 3 are often mistaken for hematomas due to their bruised appearance and they are often poorly circumscribed.<sup>20</sup> The dermal lesions tend to be variable in size depending on their location and can sometimes have small areas of necrosis and ulceration that extend into the subcutaneous tissues, which are often painful when this is present.<sup>9</sup> Clinical stage is also indicative of metastatic potential, prognosis following treatment, and survival time.<sup>20</sup> Hemangiosarcoma contained to the dermis in stage 1 has a mean survival time of 780 days, whereas the mean survival times of stage 2 and 3 are 172 and 307 days respectively. Metastasis of the cutaneous form appears to be rare in cats, though recurrence is common, with the most common site of metastasis being the lungs.<sup>10</sup> The dermal form of hemangiosarcoma also has a more favorable prognosis than the visceral form.<sup>12</sup>

To achieve a definitive diagnosis, typically a surgical biopsy is needed for histopathology. Fine needle aspiration can be used, though it has lower diagnostic yield due to hemodilution of the sample.<sup>8,19</sup> On cutaneous or subcutaneous lesions, a needle core biopsy can be obtained, but is not recommended for visceral lesions due to the risk of seeding and hemorrhage.<sup>19</sup> Complete surgical resection of cutaneous hemangiosarcoma, even of large tumors if they are location in a region that allows for aggressive excision, has a favorable long-term prognosis.<sup>9</sup>

### **History and Presentation:**

Lady, an approximately 12-year-old, spayed female Domestic Shorthair cat, was initially presented to her primary veterinarian on December 13<sup>th</sup>, 2019 for slight lethargy and defecating under the owner's bed. On physical exam, the veterinarian noted a mass on the ventral aspect of Lady's tail. On December 19<sup>th</sup>, 2019 an excisional biopsy of the subcutaneous mass was performed and the sample was submitted to Auburn University for histopathologic evaluation,

which was then reported as an undifferentiated angiosarcoma with unclear margins. Lady was then referred to the MSU-CVM Oncology Service for further staging and treatment options.

Lady was presented to the MSU-CVM Oncology Service on January 28<sup>th</sup>, 2020. On physical examination, Lady was bright and alert, though nervous. She weighed 5.35 kg with a body condition score of 6/9. Her heart rate was 240 beats per minute, respiration rate was 60 breaths per minute, and her mucous membranes were pink with a capillary refill time of less than 2 seconds. She had irregular iris margins of both eyes, her peripheral lymph nodes palpated normally, and her abdomen was tense on palpation but was non-painful. Thoracic auscultation was within normal limits and did not reveal any murmurs, arrhythmias, crackles, or wheezes. There was also a scab found on the ventral aspect of her tail. The remainder of her physical exam was within normal limits. Lady underwent an abdominal ultrasound and thoracic radiographs to look for metastasis of the undifferentiated angiosarcoma. The radiographs showed no evidence of thoracic metastasis, but the ultrasound found a non-obstructive colonic mural nodule, which was then aspirated for cytology and diagnosed as a mast cell tumor. No evidence of angiosarcoma metastasis was found. Lady was then given an injection of dexamethasone and placed on omeprazole to protect against potential side effects from the mast cell tumor aspiration.

Following her oncology consultation, Lady was presented to the MSU-CVM Surgery Service on February 5<sup>th</sup>, 2020 for consultation for a tail amputation and a colonic resection and anastomosis. On presentation, Lady was bright and alert, though nervous. She weighed 5.09 kg with a body condition score of 6/9. Her temperature was 101.2°F, heart rate was 200 beats per minute, respiration rate was 44 breaths per minute, and her mucous membranes were pink with a capillary refill time of less than 2 seconds. Thoracic auscultation was within normal limits and

did not reveal any murmurs, arrhythmias, crackles, or wheezes. Lady's iris margins were irregular and abdominal palpation was within normal limits. A small scar about 1 cm in diameter was noted on the ventral aspect of the base of her tail consistent with her history of previous mass excision. The remainder of the exam was within normal limits.

### **Diagnostic Approach/Consideration:**

In felines with the cutaneous form of an angiosarcoma, it is recommended to perform a complete blood count (CBC) and serum chemistry profile, along with thoracic radiographs and abdominal ultrasound to evaluate for metastasis.<sup>10,12</sup> Fine-needle aspiration or biopsy of regional lymph nodes can also be used in detecting metastasis. Regional imaging of the tumor with a CT or MRI (magnetic resonance imaging) can also be performed to help plan for surgery and is useful for staging local disease. Other regional imaging modalities useful for staging the local tumor depending on its location include radiographs, ultrasonography, angiography, and nuclear scintigraphy. Diagnosis of a soft tissue sarcoma can be obtained through either an FNA or biopsy. However, with an FNA cytology may be non-diagnostic due to the poor exfoliation of cells or necrosis, so a biopsy is often necessary.<sup>20</sup>

Histologically, hemangiosarcoma and lymphangiosarcoma resemble each other. However, lymphangiosarcoma often lacks red blood cells within the vascular space. There are also immunohistochemical markers that can be used to differentiate lymphangiosarcoma from hemangiosarcoma, including Factor-VII associated antigen, prospero-related homeobox gene-1 (PROX-1), lymphatic vessel endothelial receptor – 1 (LYVE-1), vimentin, and cytokeratin.<sup>17,16</sup>

### **Pathophysiology:**

An undifferentiated angiosarcoma can be further classified as either a lymphangiosarcoma or hemangiosarcoma. The incidence of lymphangiosarcoma in cats appears

to be very rare, with one study suggesting that it makes up about 0.06% of all neoplasms in cats and the biologic behavior of lymphangiosarcoma is not well described.<sup>19</sup> The clinical signs of the two types are very similar and both express a higher rate of metastatic potential than other soft tissue sarcomas.<sup>17,20</sup> Soft tissue sarcomas arise from mesenchymal tissues, with lymphangiosarcomas and hemangiosarcomas originating from lymphatic and vascular endothelial cells respectively.<sup>20</sup>

The exact etiology of hemangiosarcoma is not well understood in dogs and cats. Cutaneous lesions typically occur on the head, muzzle, ears, ventral abdomen, and other areas of thin hair or light-colored pigmentation. This suggests that solar radiation exposure and pigmentation characteristics are potential predisposing factors.<sup>7,15</sup> Cutaneous hemangiosarcoma has been experimentally induced in dogs exposed to UV radiation.<sup>9</sup> Other sources of radiation can lead to an increased risk of developing visceral hemangiosarcoma.<sup>15</sup> Dogs exposed to ionizing radiation has been documented to increase risk of hemangiosarcoma development.<sup>19</sup> There have also been reports of hemangiosarcoma development in humans that have been exposed to thorium dioxide, arsenicals, vinyl chloride, and androgens.<sup>19</sup> The presence of breed predispositions in dogs suggests a genetic component, though there have been no specific genetic mutations found associated with hemangiosarcoma.<sup>15</sup>

However, dysregulation of molecular pathways governing angiogenesis may be an important factor in hemangiosarcoma pathogenesis. Studies have shown abundant expression of angiogenic growth factors in hemangiosarcoma cells and tissues and their associated cellular receptors. Such growth factors include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and angiopoietins-1 and -2 (Ang-1 and -2). This indicates a potential for autocrine stimulation of any of these receptors leading to dysregulated stimulation.<sup>19</sup>

Increased expression of VEGF 121 in an endothelial cell line from primary murine cells leads to the development of malignant transformation.<sup>2</sup> Rats administered riddelliine, a suspected carcinogen, had an increase in hemangiosarcoma development.<sup>4</sup> Riddelliine alters the function of hepatocellular and endothelial cells by increasing stimulation of VEGF leading to dysregulation and cell proliferation causing development of hemangiosarcoma.<sup>11</sup>

One study found that the tumor suppressor gene PTEN was inactivated in more than half of hemangiosarcoma samples.<sup>12,19</sup> Studies have also shown mutations in other tumor suppressor genes such as p53, Ras, and Tsc2 can cause hemangiosarcoma development. Growth and apoptosis regulating proteins have also appeared to be overexpressed in hemangiosarcomas, including pRB, cyclin D1, BCL2, and survivin.<sup>19</sup> The tumor suppressor protein, p53, plays a role in suppressing cell growth and tumor formation in response to DNA damage. One study concluded that disruption of the function of p53 likely plays a role in the formation of certain feline tumors, including hemangiosarcomas, however only 1 out of 7 hemangiosarcomas in this study showed p53 nuclear staining. This suggests that the gene may be uncommon in feline hemangiosarcoma.<sup>13,15</sup> There is also a possibility that cutaneous hemangiomas can progress to hemangiosarcoma due to repeated genetic damage.<sup>15</sup>

### **Treatment and Management Options:**

The recommended treatment for angiosarcoma (lymphangiosarcoma and hemangiosarcoma) is wide surgical resection. Since soft tissue sarcomas are very locally aggressive, the most important consideration is local tumor control, with surgical resection being the primary treatment.<sup>20</sup> The recommended surgical margins for soft tissue sarcomas are 3 cm lateral to the tumor and one fascial layer deep to the tumor. To achieve adequate surgical margins and local control, radical surgery such as with limb amputation may be necessary.

Radiation therapy may also be used in local control, especially in tumors that are incompletely resected or unable to be resected. The recommended chemotherapy following surgery for soft tissue sarcoma is doxorubicin, especially in those with higher metastatic potential, such as with hemangiosarcoma and lymphangiosarcoma.<sup>20</sup>

In nonresectable stage 2 and 3 cutaneous hemangiosarcomas, approximately 40% of dogs treated with doxorubicin showed a median response duration of 53 days. It may also downstage the tumors and decrease their size to allow for complete surgical resection. In dogs with subcutaneous and intramuscular hemangiosarcomas treated with surgical resection and doxorubicin have a median disease-free interval and survival time of 1553 and 1189 days and 266 and 273 days, respectively. Cutaneous hemangiosarcomas in cats often have poor local tumor control following surgical resection, with a 50-80% local recurrence rate which occurred at a median of 420 days following surgery. However, the mean survival time following wide surgical resection in cats is 1460 days, whereas untreated cats had a mean survival time of 60 days.<sup>20</sup>

The MSU-CVM Surgery Service performed a complete blood count and chemistry panel. The CBC revealed a leukopenia (3.56 /ul with a reference range of 5.5-20 /ul) characterized by a lymphopenia (676 /ul with a reference range of 1500-7200 /ul), and hemoglobin was very slightly elevated (13.1 g/dl with a reference range of 9-13 g/dl). The chemistry panel showed an elevated creatinine (2.72 mg/dl with a reference range of 0.4-2 mg/dl) and a slightly elevated albumin (3.3 g/dl with a reference range of 2.2-3.2).

Lady then underwent surgery with the MSU-CVM Surgery department on February 6<sup>th</sup>, 2020. First, a colonic resection and anastomosis was performed to remove the mast cell tumor. Then she was prepped for a high tail amputation to allow for 2-3 cm margins around the tumor.



The distal tail was wrapped with sterile vet wrap to protect the sterile surgical field. The margin of the scar from the previous mass excision on the ventral proximal tail were marked using a surgical marking pen. A 2 cm margin was then measured proximally to the mass and was marked with the same pen. A tourniquet was placed proximal to the surgical site at the base of the tail using a penrose drain. Two semilunar incisions were then made on the dorsal and ventral tail with the peak of the curve at about the 3 cm margin. The subcutaneous tissues and muscles of the tail were dissected to expose the vertebra caudal to the semilunar flaps created by the incisions. 3-0 PDS was used to ligate the lateral caudal and medial caudal arteries, and a scalpel blade was inserted into the intervertebral space of the joint to be disarticulated. The joint was then disarticulated and the tail was removed. The tourniquet was then released to inspect for bleeding and bleeding vessels were cauterized. The muscle layer was closed over the exposed vertebrae with 3-0 PDS in a cruciate pattern. The subcutaneous tissue was closed over the tail stump using 3-0 Monocryl in a simple interrupted buried pattern. The skin was then closed using 3-0 nylon suture and a simple interrupted pattern.<sup>5</sup>

Histopathologic results from the surgical samples submitted for biopsy concluded that the tumor on Lady's tail was a hemangiosarcoma and confirmed diagnosis of a mast cell tumor of her colon. Both tumors were completely excised. Following surgery for hemangiosarcoma, doxorubicin-based chemotherapy is most frequently used, though vincristine, cyclophosphamide, and methotrexate have also improved survival time.<sup>19</sup> However, Lady was a unique case in that she had both a hemangiosarcoma and mast cell tumor. Because of this, Lady's chemotherapy agent was vinblastine to target the mast cell tumor, since metastasis of intestinal mast cell tumors is common in cats.<sup>18</sup> Radiation therapy may help decrease local disease in feline cutaneous and subcutaneous hemangiosarcoma, especially in those with incompletely resected masses.<sup>19</sup>

There are also novel therapies that are not well-studied at this time or are not currently available. Immunotherapy with liposomal muramyl tripeptide phosphatidylethanolamine, when given in conjunction with a doxorubicin and cyclophosphamide protocol, improved survival time. However, this treatment is not available in the United States.<sup>12,19</sup> A study using a xenograft model determined that IL-12 suppressed angiogenesis and tumor growth of hemangiosarcoma cells.<sup>1</sup> Other antiangiogenic treatments, such as with VEGF receptor kinase inhibitors and TNP-470 has been shown to have antitumor activity in murine hemangiosarcoma models.<sup>19</sup>

**Case Outcome:**

Lady was discharged from the MSU-CVM Surgery Service on February 10<sup>th</sup>, 2020. At that time, she was sent home on buprenorphine and gabapentin. She returned on February 28<sup>th</sup> for an incision recheck and to recheck her renal values. The owner reported Lady was doing very well recovering at home. On presentation, both of her incision sites were healing appropriately and blood was drawn for a renal profile. Initially the results showed a low albumin, so an A-FAST (abdominal focused assessment with sonography for trauma) scan was performed to look for any abdominal fluid, but none was noted. The renal profile was requested to be rerun and the new results showed no significant findings. The creatinine value, which was previously elevated at the time of surgery, was also normal at this time (1.52 mg/dl with a reference range of 0.4-2 mg/dl).

Lady then returned to the MSU-CVM Oncology Service on March 4<sup>th</sup>, 2020. At that time a CBC was performed and Lady was administered her first dose of vinblastine. She was sent home the following day with metronidazole and ondansetron to be used as needed if gastrointestinal side effects were to occur from the chemotherapy treatment. Lady returned for her 1-week chemotherapy recheck on March 11<sup>th</sup>, 2020. Her owner reported that she had been

vomiting and having diarrhea since her last visit. A complete blood count showed grade 4 neutropenia. Lady was treated with subcutaneous fluids and given a maropitant injection. She was then sent home on clavamox, maropitant, metronidazole, and ondansetron with instructions to return in 1 week for another CBC and to continue vinblastine at a reduced dose if appropriate.

Due to the circumstances regarding the human COVID-19 outbreak, Lady continued her follow-up care and chemotherapy at her primary veterinarian. It was then reported on May 11<sup>th</sup>, 2020 that Lady continued to have severe side effects from the chemotherapy and was not doing well at home, so her chemotherapy was discontinued. On July 18<sup>th</sup>, 2020 Lady was reported to be doing very well at home since the chemotherapy has been discontinued and is back to her usual self. The owner is very happy with how Lady is doing now.

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