Salty, Bad to the Bone

Cody D. Faulkner

Mississippi State University College of Veterinary Medicine

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Taya M. Marquardt, DVM, MS, DACVIM (Onc)

CPC Advisor

Introduction

Canine hemangiosarcoma is an aggressive and malignant neoplasia of endothelial cells with a grave prognosis. There is about a 7% occurrence of hemangiosarcoma in the dog. The dog is the most common species for hemangiosarcoma to manifest (Sorenmo, 2004). German Shepherds, Golden Retrievers, Labrador Retrievers, and Schnauzers are predisposed, but any dog breed can be affected. A sex predilection has not been proven. It is rarely curable due to local infiltration and distant metastasis early in the disease process. Even with aggressive treatment, patients often succumb to disease within 4 to 6 months of diagnosis due to drug resistant metastatic disease (Sorenmo, 2000). Treatment mainly consists of surgery followed by intravenous chemotherapy. The three main locations hemangiosarcoma manifests are right atrium, spleen, and skin. They are rarely found within the bone.

Most patients with bone lesions present with signs of pain, lameness, and swelling due to destruction of the bone. These clinical signs could be associated with a few differentials. Neoplasia was the top differential with bacterial or fungal osteomyelitis being less likely. The majority of bone tumors in the dog are malignant with guarded prognosis. The most common bone tumor is osteosarcoma (approximately 85%), with chondrosarcoma (approximately 10%), fibrosarcoma (approximately 5%), and hemangiosarcoma (approximately 5%) being less common (Watson, 2002). Osteosarcoma and hemangiosarcoma metastasize early in the disease process worsening their prognosis. On histopathology, hemangiosarcoma can look very similar to telangiectatic osteosarcoma. Normally they can be differentiated on routine histopathology alone, but telangiectatic osteosarcoma can have a small amount of osteoid present appearing similar to hemangiosarcoma. Histopathology with immunohistochemistry for endothelial cell

marker factor VIII-related antigen/von Willebrand factor can help differentiate between hemangiosarcoma and telangiectatic osteosarcoma when warranted (Giuffrida, 2016).

Patient History

Salty was a 12-year-old male neutered West Highland Terrier who presented to MSU-CVM Oncology Department on June 19, 2018 for an oncology consultation for a primary hemangiosarcoma tumor of the right femur that had been amputated by Animal Emergency & Referral Center. On April 25, 2018, he was diagnosed with a right cranial cruciate tear and radiographs revealed no bony changes to the femur. Two days before his scheduled surgery date, he became very painful and non-weight bearing on his right hindlimb, and the owners appreciated a clicking sound. The owners gave tramadol which seemed to help. On May 15, 2018, a lateral suture repair was performed to correct his cranial cruciate rupture. A cast was placed and he remained non-weight bearing lame during this time. On May 25, 2018, the cast was removed and the incision site was healing well. The owner noticed a small amount of abdominal bruising two days after the removal of the cast. He presented to Animal Emergency & Referral Center on May 28, 2018 for right hindlimb lameness and abdominal bruising. Radiographs of the right femur were performed and revealed an aggressive lytic lesion, which was suspected to be a bone tumor. There was a pathologic fracture with proximal and caudal displacement present. The top differential at that time was primarily neoplasia, osteosarcoma being most likely, with lesser consideration given to fungal or bacterial osteomyelitis. On May 29, 2018 a right hindlimb amputation was performed and a biopsy was submitted. The histopathology results revealed primary hemangiosarcoma of the femur. Salty seemed to be recovering well from his amputation. Salty was referred to MSU-CVM Oncology Department to pursue further diagnostics and treatment.

Clinical Presentation

Upon presentation, Salty was bright, alert, and responsive. His physical exam revealed normal vital parameters (temperature = 101.4* F, pulse = 130 beats/minute, and respiratory rate = 20 breaths/minute). His lungs auscultated normally. Auscultation of his heart revealed a respiratory sinus arrhythmia (normal in dogs), but no murmurs. His mucous membranes were pink and moist with a normal capillary refill time of less than 2 seconds, indicating adequate hydration. Oral examination revealed mild dental tartar. Nuclear sclerosis was present bilaterally. Abdominal palpation revealed a soft abdomen with no pain or other obvious abnormalities noted. A 5x5 mm black mass was present on his rectum. Peripheral lymph nodes were within normal limits. The incision from his right hindlimb amputation had healed appropriately. He appeared to ambulate well on three limbs. The remainder of his physical examination was unremarkable.

Diagnostic Approach & Considerations

A biopsy was submitted after amputation, and Salty was diagnosed with femoral hemangiosarcoma with pathologic fracture of the diaphysis. It can be difficult to differentiate hemangiosarcoma of the bone and telangiectatic osteosarcoma as both are distinguished by the presence of cell-lined blood-filled cystic spaces. The difference is seen in the cystic spaces as hemangiosarcomas are lined with malignant endothelial cells and telangiectatic osteosarcomas are lined with malignant osteoblasts. If the biopsy sample is too small or osteoid matrix is not present, it can be difficult to differentiate with routine histopathology alone. Factor VIII-related antigen immunohistochemistry has been shown to be reliable diagnostic tool for differentiating the two sarcomas (Giuffrida, 2016). The factor VIII-related antigen is not expressed by osteoblasts, so a positive immunoreactivity reinforces a diagnosis of hemangiosarcoma. It is important to differentiate due to different staging and treatment approaches. Telangiectatic

osteosarcoma's staging consists of thoracic radiographs where as hemangiosarcoma consists of thoracic radiographs and abdominal and cardiac ultrasound due to the affinity of metastasis to certain areas of the body. This is a beneficial diagnostic tool for differentiating especially for samples that do not have overtly evident osteoid proliferation (Giuffrida, 2016).

Based on Salty's history, it was recommended to the owner to stage him to look for any evidence of metastasis prior to starting any chemotherapy. A complete blood count (CBC), chemistry, and coagulation profile were performed. The CBC revealed a mild lymphopenia and a mild eosinophilia. The chemistry revealed a mild azotemia. The coagulation profile was within normal limits. Based on the azotemia, it was recommended to perform a urinalysis to determine if the azotemia was related to his kidneys or dehydration. A urinalysis revealed mildly unconcentrated urine and 1+ protein present in the urine. These results were suggestive of early kidney disease, but more diagnostics were needed for a definitive diagnosis. At that time, it was decided to monitor as this would not affect chemotherapy. Thoracic radiographs revealed no evidence of nodular pulmonary metastasis. Abdominal radiographs revealed no obvious abnormalities. On abdominal ultrasound, a large gallbladder with hyperechoic material and hypoechoic nodules, bilaterally mineralized kidneys, and an enlarged right iliac lymph node were seen. No abdominal or heart-based masses were seen. His fractional shortening was normal meaning his ventricles were contracting appropriately. In summary, no macrometastasis was noted during the staging process. The enlarged right iliac lymph node was the only thing that was suspicious, but due to its location next to the aorta, it was risky to aspirate. With these findings, Salty was determined to be a good candidate for chemotherapy.

Pathophysiology

Canine hemangiosarcoma is a malignant tumor arising from the endothelium of blood vessels. The etiology of hemangiosarcoma is unknown, though it has been associated in certain breeds suggesting a familial predisposition. Cutaneous hemangiosarcoma is thought to be associated with ultraviolet light exposure in lightly pigmented dogs. Hemangiosarcoma in humans has been associated with exposure to thorium dioxide or arsenical or vinyl chloride compounds (Clifford, 2000).

Since hemangiosarcoma is a neoplasm of the blood vessels, it has the potential to manifest anywhere in the body. The 3 common primary sites are spleen (28-50%), right atrium and auricle (3-50%), and skin (13%) (Clifford, 2000). Primary hemangiosarcoma of bone is rare, and the incidence is reportedly less than 5% of all primary canine bone tumors (Watson, 2002). The bones most commonly affected are proximal humerus, rib, femur, and vertebrae. Primary hemangiosarcoma of bone typically destroys extensive areas of normal bone architecture but does not usually cause bone proliferation or soft tissue swelling like osteosarcoma. Pathologic fractures are common due to the amount of bone destruction, and usually is the cause of the first clinical sign. The most common clinical signs are similar to other bone tumors including pain, lameness, and occasionally soft tissue swelling (Goldschmidt, 1985).

Due to the vascular nature of hemangiosarcoma, metastasis and local invasion occur early in the disease process. Along with hematogenous metastasis, local seeding can occur after tumor rupture. Hemangiosarcoma metastasizes early and rapidly throughout the body, most commonly to the lungs, liver, peritoneum, and central nervous system (Finotello, 2016). Hemangiosarcoma is rarely curable and long-term prognosis for dogs with hemangiosarcoma is poor. Dogs treated with surgery alone have a median survival time around 3 weeks to 2 months, where as dogs

treated with surgery and chemotherapy have an increased median survival time of 3 to 6 months (Sorenmo, 2000).

Treatment and Disease Management

Surgery is usually the first step of treatment for hemangiosarcoma. If surgery alone is performed, there is little improvement in survival time. It is more of a palliative treatment to decrease pain and the chance of hemorrhage. Because of the limitations of surgery alone, the main focus of treatment has become chemotherapy. There are various protocols based on doxorubicin. Doxorubicin can be used as a single agent or be combined with vincristine or cyclophosphamide. These have shown to have the best survival time. No particular doxorubicin-based protocol has been shown to be superior. The median survival time of the different protocols is 4 to 6 months (Clifford, 2000).

Based on the high metastatic rate, chemotherapy was recommended. In Salty's case the specific chemotherapeutic we recommended was doxorubicin as a single agent protocol. Doxorubicin can cause severe tissue damage and possible sloughing if any chemotherapy gets out of the vein, which may result in the need for an amputation. This was extremely important in Salty's case, because he already had a limb amputated, so the need for another amputation would likely be the end. Due to the risks associated with doxorubicin, the owner elected for metronomic therapy.

Metronomic therapy is a continuous administration of fixed, low doses of chemotherapy drugs without prolonged breaks in treatment (Lana, 2007). The metronomic protocol consisted of cyclophosphamide 13 mg/m^2 PO q24h and piroxicam 0.3 mg/kg PO q24h. Cyclophosphamide is an alkylating agent that inhibits proliferation along with promoting apoptosis of activated endothelial cells and inhibition of regulatory T lymphocytes. Piroxicam is a non-selective

nonsteroidal anti-inflammatory that has an antiangiogenic effect. It is thought to enhance the activity of cyclophosphamide. Piroxicam is traditionally used for patients with transitional cell carcinoma (Elmslie, 2008). A study has shown that a low dose chemotherapy protocol consisting of cyclophosphamide, etoposide, and piroxicam yields comparable results to the conventional maximum-tolerated dose chemotherapy. This study is suggestive of this protocol being used to delay disease progression in hemangiosarcoma (Finotello, 2016). Another study has shown that treating a soft tissue sarcoma with cyclophosphamide and piroxicam was very effective in inhibiting the regrowth of microscopic tumor foci in dogs (Elmslie, 2008). The most common adverse effects seen with piroxicam are primarily gastrointestinal ulcerations or bleeding and increased renal values. A known complication of cyclophosphamide is sterile hemorrhagic cystitis (Finotello, 2016).

Salty's owner was very interested in supplements and other holistic approaches in addition to the metronomic therapy. In addition to changing his diet, Salty's owner started supplements before his visit with MSU-CVM. After discussing with the owner about the lack of scientific research with certain supplements, I'm Yunity and Yunnan Baiyao were recommended. I'm Yunity is a polysaccharopeptide product derived from a Chinese medicinal mushroom. It has been shown to demonstrate a decrease in tumor proliferation and an increase in apoptosis in vitro. Yunnan Baiyao is another Chinese herbal medicine that has been used in veterinary medicine to control bleeding. It is thought to improve clotting times and platelet function. It has been used in Chinese medicine for wound healing and as an antihemorrhagic agent in humans (Chaikin, 2018). Several components of Yunnan Baiyao have been shown to have anti-neoplastic properties, but the product as a whole needs more studies to prove its efficacy. One of the components in Yunnan Baiyao is *Panax notoginseng* root extract which has demonstrated

growth inhibition and increased apoptosis of cancer cells in vitro (Wirth, 2016). There is potential for the use of I'm Yunity and Yunnan Baiyao together with metronomic chemotherapy in patients with metastatic hemangiosarcoma.

Case Outcome

Salty was prescribed cyclophosphamide and piroxicam on June 21, 2018. He was scheduled to return for a recheck CBC, serum chemistry, and urinalysis 2 and 4 weeks after starting the medications. Re-staging was scheduled for every 2 to 3 months to monitor for disease progression, and to assess the response to chemotherapy. At Salty's first recheck, the owner reported he had vomited the day before presentation. His serum chemistry revealed a mild azotemia (BUN 46 mg/dl, Crea 1.43 mg/dl) which was unchanged from his last visit. At this time his piroxicam was switched to every other day dosing with the addition of omeprazole. His second recheck revealed a slightly increased BUN at 52 mg/dl. Due to the continuation of the mild azotemia, the piroxicam was continued at an every other day dosing.

On August 9, 2018, Salty was exhibiting neurologic signs of circling to the left and conscious proprioceptive deficits on the left. After consultation with the neurology service, it was determined he had developed left central vestibular disease. His CBC revealed a moderate anemia and thrombocytopenia. These findings were suggestive of gastrointestinal bleeding secondary to the piroxicam. The chemistry revealed azotemia (BUN 87 mg/dl, Crea 1.46 mg/dl), which has steadily increased at each appointment. The urinalysis revealed 2 + protein and a large amount of blood in the urine. Radiographs revealed presumed metastasis to his lungs and bony lysis of the right ischial wing. An abdominal ultrasound revealed newly enlarged right medial iliac and jejunal lymph nodes along with two nodules identified within the spleen. The aspirates of the spleen were nondiagnostic. At this visit, it was suspected that Salty's hemangiosarcoma

had metastasized to his lungs, right ischium, spleen, abdominal lymph nodes, and central nervous system. The metronomic therapy was discontinued at this visit due to the advancement of disease during treatment. Salty was prescribed sucralfate as a gastroprotectant due to his potential GI bleed. Further imaging was declined to definitively diagnosis the vestibular disease. Doxorubicin was discussed again as a potential next step in treatment, but the owner declined due to the extent of metastasis.

The owner continued to take Salty to Dr. Kennedy to monitor his renal values and progression of disease. After the owner did her own research, she wanted to try a nontraditional drug, rapamycin. Rapamycin is an immunosuppressive drug used in human medicine to prevent rejection of organ transplants. More studies are needed, but it is thought to inhibit the mTOR pathway that some cancers express (Paoloni, 2010). It was discussed with her that there is not a lot of evidence backing the use of rapamycin, but it was a medication we could try. Salty was prescribed 0.1 mg/kg PO MWF. The owner also started milk thistle, omega-3, apocaps, cocuten, pet-tinc, and lung gold supplements. Salty was continuously declining and he was taken to receive acupuncture. The owner reported Salty having more energy. Unfortunately, this only lasted for a few days, and on August 28, 2018 Salty was humanely euthanized.

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