“Winston’s Woes”

A Case of Canine Osteosarcoma

Hannah Urig

Mississippi State University College of Veterinary Medicine

Class of 2020

Clinicopathologic Conference

July 26, 2019

Advisor: Taya Marquardt, DVM, MS, DACVIM (Onco)

Introduction

Osteosarcoma is the most common primary bone tumor of canines and felines, and accounts for approximately 85% of all canine skeletal tumors.[1,5] Due to the locally invasive and highly metastatic nature of this disease, canine osteosarcoma generally carries a poor prognosis, with treatment options being mostly combination therapy, including surgery and chemotherapy to relieve pain and improve quality of life. Regardless of treatment, patients often succumb to disease within 12 months of diagnosis. Rarely curative, the main goal of treatment is palliation of pain and lameness by keeping the patient comfortable and pain-free as long as possible. Treatment options often include a combination of analgesics, radiation therapy or limb amputation, followed by an adjunctive chemotherapy protocol. Following diagnosis, it is important to monitor for changes in respiration, which may indicate further progression of the disease, pulmonary metastasis and decline in quality of life.

History and Presentation

Winston, an approximately 9-year old male neutered Rottweiler, presented to Mississippi State University-Animal Health Center Oncology Service on September 24, 2018 for a consultation for a right stifle mass. Winston's owner reported that he had developed a right rear lameness that had progressively worsened over the past three weeks. Winston first presented to his referring veterinarian in August 2018 for right hindlimb lameness and non-weightbearing lameness of the left stifle with a previous diagnosis of arthritis. Radiographs of the right stifle were performed and revealed lytic and proliferative lesions of the right proximal tibia. Three thoracic view radiographs were also performed revealing possible metastasis to the lungs. At that time, it was recommended that Winston be rested for two weeks and given Rimadyl every twelve

hours as prescribed. Despite medical management, Winston continued to act painful and became increasingly lame. Due to the suspicion of osteosarcoma of the right stifle with possible metastasis to the lungs as well as a prior diagnosis of cutaneous malignant melanoma (June 2018), Winston was referred to MSU-CVM Oncology Service to pursue further diagnostics.

On initial presentation, Winston was bright, alert, and responsive but very anxious. A limited physical examination was performed due to the patients' temperament, revealing normal heart and lung sounds as well as a right stifle mass. Winston was mildly hyperthermic (temperature: 103.0 °F), tachycardic (pulse 104 beats per minute), and had a normal respiratory rate (36 breaths per minute). His heart and lungs auscultated normally with no murmurs, arrhythmias, crackles or wheezes heard. The mass associated with his right stifle was firm and measured 6.5 cm x 7 cm. After observation of Winston's gait, it was noted that he was intermittently toe-touching lame on his right hindlimb. No peripheral lymphadenopathy was noted. No masses were noted in the oral cavity or associated with any digits. A soft, freely-moveable, well-demarcated mass was palpable on the lateral side of his left stifle. The remainder of the physical examination was unremarkable. Based on signalment, history, and physical exam findings, the primary differential, was a primary bone tumor, such as osteosarcoma or chondrosarcoma. Further diagnostic tests would be necessary to prove this presumptive diagnosis and guide therapeutic recommendations.

Diagnostic Approach

A minimum database for general health assessment (CBC, chemistry panel, urinalysis) was performed, revealing that Winston was an acceptable candidate to undergo sedation. A complete blood count (CBC) revealed a stress leukogram, which is commonly seen in canines

with chronic illness. His chemistry panel revealed a mildly elevated alkaline phosphatase (ALP), increased globulin, a mild hypercholesterolemia, and a mild hypomagnesemia. Of these results, the elevated alkaline phosphatase can be seen as a negative prognostic indicator in osteosarcoma cases due to its production in osteoblasts. Thoracic radiographs were performed and there was no evidence of metastatic nodular pulmonary neoplasia. Repeat radiographs of the right stifle were then performed, revealing an aggressive boney lesion at the right proximal tibia that measured approximately 12 x 17 mm. A fine needle aspirate of this boney lesion was obtained and sent for cytological evaluation. Results of the cytology were consistent with a non-epithelial malignant tumor.

Based on the results of the cytological evaluation, Winston was diagnosed with cancer of his right proximal tibia. Amputation of his leg was discussed with his owner in order to provide the best chance at controlling the pain this tumor causes (through breakdown of the bone) as well as controlling the local progression of the tumor. Histopathology could then be performed to determine the type of cancer, allowing for the selection of chemotherapy that would best target the specific type of cancer cells. Further discussion of the most likely diagnosis for this cancer is osteosarcoma. A consultation with the surgical service was recommended for additional assessment of his orthopedic examination, and to potentially pursue amputation of the leg.

With the strong suspicion for osteosarcoma, Winston's owners decided to pursue consultation with the Surgical Service at MSU-CVM. Winston presented to MSU-CVM Surgery Services on September 27, 2018 for right hindlimb lameness. Orthopedic examination revealed a 2/5 lameness in his right hindlimb when walking. The bony mass in the area of the right stifle made flexion and extension painful. On the left stifle, there was significant buttress. The left stifle appeared locked in a cranial drawer position, and the femur and tibia could be felt

contacting each other in motion. Due to owner concern, it was decided to forgo amputation and instead Winston underwent a core biopsy of the right proximal tibia. Due to Winston's prior diagnosis of cutaneous malignant melanoma it was also decided that Winston undergo a right submandibular lymph node extirpation to determine if there was metastasis caused by the melanoma or another form of neoplasia. Surgery went without complication and recovery from anesthesia was uneventful.

Pathophysiology

Canine osteosarcoma (OSA) is a malignant tumor of the mesenchymal cell origin and is considered to be the most common form of malignant appendicular skeletal cancer in dogs.[1] OSA in dogs shares many biological similarities to human osteosarcoma, but evidence shows that the disease occurs 10 times more frequently in dogs than in people. As the most commonly diagnosed primary bone tumor in dogs, it is responsible for approximately 85% of aggressive bone tumors.[2] OSA tumors are commonly associated with the long bones of the appendicular skeleton, particularly near the metaphyseal growth plates. The distal radius and proximal humerus are the two most common locations for OSA tumors in canines; however, the distal femur, proximal tibia and proximal humerus are also commonly affected.[1] Differing clinically in presentation, human OSA typically occurs adolescence during the pubertal growth spurt stage, while canine OSA occurs more commonly in middle-aged to older dogs following physeal closure.[1,3]

Historically, the incidence of OSA in both humans and canines was considered to be higher in males, however current research shows that the two most predictive factors in the development of OSA in canines are increasing weight and tall shoulder height. Large and giant

breed dogs, such as Rottweilers, Greyhounds, Great Danes, Saint Bernards and Irish Wolfhounds have a higher incidence of inherited risk factors associated with this disease.[1] Current research further demonstrates a relationship with bone growth and pathogenesis of OSA with the expression of insulin-like growth factor-1 (IGF-1) in the cells of canine OSA.[1,4] This likely plays a role in the complex etiology of OSA, involving environmental and physical factors, genetic susceptibility and acquired molecular changes.

Clinical presentation of OSA is seen as a history of lameness and swelling at the primary site. As an aggressive tumor, a defining feature of canine OSA is its high rate of metastasis. The primary bone tumor disseminates quickly through hematogenous spread, with the development of metastasis seen primarily in the pulmonary parenchyma. Metastasis can also be seen in regional lymph nodes, other bones or soft tissue structures. Locally, soft tissue swelling, and pathologic fractures of affected bone are commonly seen due to the weakening of the bone caused by the tumor. Radiographically, defining features of OSA are described as a “sunburst” pattern consisting of boney lysis and new boney proliferation. Despite not having radiographic evidence of metastasis at the time of diagnosis, 85-90% of patients develop gross metastasis indicating subclinical micromeastases to the pulmonary parenchyma occurring early in the pathogenesis of disease.[1,5]

Reported treatments for OSA in both canines and humans include, aggressive surgical techniques, palliative radiotherapy, chemotherapy, or a combination of these therapies. However, despite the type of treatment initiated in canine patients with OSA, treatment is considered minimally effective with long-term survival rates of 10-15%.[1,3,5] OSA tumors are classified based on location, cell type (>50% of the malignancy), and tumor grade. Therapy directed at the primary bone tumor includes surgical options such as amputation and limp-sparing procedures.

Removal of the affected limb resolves the pain; however, median survival time with amputation alone is 3-6 months. In 40-50% of canine patients that received chemotherapy in conjunction with surgical amputation, the median survival time was 262- 413 days.[6] The most effective therapy of OSA and metastatic disease involves a multimodality therapeutic approach. In canine patients, carboplatin chemotherapy (as either a single-agent or multi-agent protocol), in combination with doxorubicin has been demonstrated to improve survival time following amputation.[3, 6] As a nonsurgical limb-sparing alternative, radiotherapy or stereotactic radiotherapy can be utilized for palliation of bone pain. Stereotactic radiation treatment delivers high doses of radiation to a tumor while sparing organs at risk through beam modulation and precise patient positioning.[7] Despite technical refinement, the primary disadvantage of stereotactic radiation therapy remains associated with its high complication rate with the most recent study reporting a 95.5% complication rate.[7] The largest complication reported was pathologic fracture, with fractures occurring in 63% of dogs that undergo this treatment.[7] Management of the progressive nature of canine OSA can also be provided through palliative analgesic medications. No single analgesic provides enough pain relief; however, a combination of analgesic medications can be considered reasonably palliative as a last resort if amputation, palliative radiation therapy or chemotherapy are not pursued.[1,5]

Treatment and Management

In Winston's case, while biopsy results confirmed diagnosis of osteosarcoma (OSA), lymph node biopsy did not contain evidence of cancer (melanoma) spread. At this time, the owner chose to pursue local control of the OSA through stereotactic radiation therapy and follow-up with chemotherapy. Winston presented to Louisiana State University (LSU) for

stereotactic radiation therapy (SRT) where he received three doses of 12 Gray SRT from October 10^{th} -12^{th}. Winston was also administered a single dose of zoledronate in an effort to manage the painful osteolytic lesions and refractory hypercalcemia.

On October 30, 2018, Winston presented to Colorado State University (CSU) Veterinary Teaching Hospital Oncology Service for continued treatment of his OSA of the right proximal tibia. Since Winston appeared to be responding well to the SRT, with decreased right hindlimb lameness and a reduction in the soft tissue swelling around the OSA lesion, the decision to initiate a 4-dose adjuvant therapy of carboplatin was started. Winston continued to receive carboplatin chemotherapy through November and December 2018.

In December 2018, thoracic radiographs were performed revealing 2 new nodules visible on the right lateral, and metastasis was suspected. Due to the suspected metastasis, performing a computerized tomography (CT) scan and switching the current chemotherapy protocol to a palladia losartan protocol was discussed with the owner. On January 23, 2019, Winston presented to CSU for CT of the thorax and right hindlimb. The CT revealed, multiple soft tissue nodules (likely metastatic neoplasia) identified throughout the pulmonary parenchyma, with the largest measuring 11 mm in diameter in the left caudal lung lobe. CT of the hindlimb revealed coxofemoral arthritis of the right hindleg and stifle arthritis of the left hindleg. The osteosarcoma site appeared to be mostly unchanged. At this time, it was determined that Winston would be a poor candidate to undergo surgical or radiation therapy. It was recommended that Winston return in 1-2 months to assess further response to the palladia chemotherapy protocol and for another CT.

On March 18, 2019, Winston presented to CSU for repeat CT scan of the right hindlimb and chest to evaluate for progression of disease for his previously diagnosed OSA. At this time,

Winston had significant drainage and swelling from a wound on the medial aspect of the right hindlimb. A full thickness skin wound, approximately 4 cm long, was noted. His owners reported that they had discontinued the palladia and losartan three weeks prior to presentation due to gastrointestinal toxicity. CT of the thorax revealed progression in size of the previously noted nodules and CT of the hindlimb revealed changes in the leg compared to the previous CT scan. Winston was started on cytoxan at a dose of 15 mg/m2. It was recommended that Winston have a repeat CT performed in 8 weeks to assess response to the new therapy.

Case Outcome

On April 30, 2019, Winston presented to MSU-CVM Oncology service for restaging and re-evaluation of his previously diagnosed osteosarcoma. On presentation, Winston was noted to be intermittently toe-touching lame on his right hindlimb and a firm, 6.5cm x 7 cm mass on his right stifle was also noted. Physical examination revealed a non-healing wound on the medial aspect of the hindlimb with visualization of the proximal tibia/tumor that contained the presence of yellow-green necrotic tissue along with odor. Moderate edema of the entire distal right hindlimb was noted, along with a small, soft, freely moveable mass on the left lateral thorax near the sternum/axillary region. A CBC, chemistry panel, and urinalysis were unremarkable. Winston was sedated prior to performing further diagnostic procedures and a detailed physical exam.

Thoracic radiographs showed a structured interstitial pattern consistent with metastatic pulmonary neoplasia. Right stifle radiographs revealed a severe circumferential osteoproliferation of the previously described aggressive bony lesion in the proximal tibial metaphysis. This was consistent with progressive osteosarcoma. Fine needle aspirates of his

multiple cutaneous masses revealed dermal metastatic osteosarcoma. Treatment options focusing on palliative care and hindlimb amputation were discussed with Winston's owners. Quality of life and guarded prognosis were also discussed. Recommendations were made to remove the right hindlimb if the owners decided to move forward with palliative/hospice care, and Winston's owners were instructed to discontinue cyclophosphamide for 1 week prior to pursuing amputation to improve wound healing. After amputation, additional chemotherapy may be considered at that time. A consultation with MSU-CVM Surgery Service was scheduled for the following week. Due to the continued progression of the osteosarcoma and poor quality of life, Winston's owners elected for humane euthanasia at their referring veterinarian's practice.

References

1. Joelle M. Fenger, Cheryl A. London, William C. Kisseberth, Canine Osteosarcoma: A Naturally Occurring Disease to Inform Pediatric Oncology, *ILAR Journal*, Volume 55, Issue 1, 2014, Pages 69–85, https://doi.org/10.1093/ilar/ilu009
2. Swift, K. E., & Larue, S. M. (2017). Outcome of 9 dogs treated with stereotactic radiation therapy for primary or metastatic vertebral osteosarcoma. Veterinary and Comparative Oncology, 16(1), 152-158. doi:10.1111/vco.12362
3. Schmidt, A., Nielen, M., Withrow, S., Selmic, L., Burton, J., Klungel, O., Kirpensteijn, J. (2016). Chemotherapy effectiveness and mortality prediction in surgically treated osteosarcoma dogs: A validation study. Preventive Veterinary Medicine, 125, 126-134. doi:10.1016/j.prevetmed.2016.01.004
4. Selvarajah, G. T., & Kirpensteijn, J. (2010). Prognostic and predictive biomarkers of canine osteosarcoma. The Veterinary Journal, 185(1), 28-35. doi:10.1016/j.tvjl.2010.04.010
5. Simpson, S., Dunning, M. D., de Brot, S., Grau-Roma, L., Mongan, N. P., & Rutland, C. S. (2017). Comparative review of human and canine osteosarcoma: morphology, epidemiology, prognosis, treatment and genetics. Acta veterinaria Scandinavica, 59(1), 71. doi:10.1186/s13028-017-0341-9
6. Bailey, D., Erb, H., Williams, L., Ruslander, D., & Hauck, M. (2003). Carboplatin and Doxorubicin Combination Chemotherapy for the Treatment of Appendicular Osteosarcoma in the Dog. Journal of Veterinary Internal Medicine, 17(2), 199-205. doi:10.1892/0891-6640(2003)0172.3.co;2

7. Boston, S. E., Vinayak, A., Lu, X., Larue, S., Bacon, N. J., Bleedorn, J. A., Ehrhart, N. P. (2017). Outcome and complications in dogs with appendicular primary bone tumors treated with stereotactic radiotherapy and concurrent surgical stabilization. Veterinary Surgery, 46(6), 829-837. doi:10.1111/vsu.12669