Ulnar Osteosarcoma

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INTRODUCTION

Osteosarcoma is the most common bone tumor seen in canine patients,[1] accounting for 85% of primary bone tumors.[2] Ulnar osteosarcomas are rare, and while several aspects are similar to more traditional osteosarcomas, these tumors have some unique diagnostic features.[1] Additionally, different treatment options are available for osteosarcomas that affect only the ulna.

HISTORY AND PATIENT PRESENTATION

Patients with ulnar osteosarcomas most commonly present with lameness as the primary complaint. Because osteosarcomas are expansile in character, the infiltration of tumor cells into surrounding connective tissue causes degradation of the bone, extensive soft tissue swelling, and significant pain. Soft tissue swelling is due to impaired circulation of the affected area that subsequently results in congestion in the surrounding tissues.[3] Pain results not only from instability of affected bones, but also from chemical mediators that are released by malignant osteolysis. Nociceptors present within the bone, primarily the periosteum and medullary cavities, are continuously activated by the release of these mediators, resulting in chronic mechanical and neuropathic pain.[4]

DIFFERENTIAL DIAGNOSES

The top differential diagnosis in large breed dogs who present with lameness, swelling, and pain associated with one limb is a primary bone tumor such as osteosarcoma or hemangiosarcoma, especially when imaging has ruled out the presence of a primary tumor elsewhere in the body. Fungal osteomyelitis such as an infection with *Coccidioides immitus* or *Blastomyces dermatitidis* is also considered, though fungal lesions are not typically isolated to the metaphyseal area of long bones as osteosarcomas are. Other considerations include bacterial osteomyelitis, atypical bone cysts, metastatic neoplasia, lymphoma, and multiple myeloma, though these diagnoses are not as likely.[5]

PATHOPHYSIOLOGY

The pathogenesis of osteosarcoma is related to the rapid growth and development of affected animals as well as inherited genes predisposing to the disease. Giant breed dogs are at a greater risk for development of osteosarcoma. Scottish Deerhounds have been shown to have a narrow heritability for the development of osteosarcoma, meaning that 70% of the time the occurrence of osteosarcoma is due to inherited traits in the breed.[2] Rottweilers have four specific regions of their genome that have been associated with increased risk of the development of osteosarcoma. Other breeds such as Labrador and Golden retrievers, Great Danes, Dalmatians, and Doberman pinschers are also at risk.[1] Genetic testing is currently being developed that can pinpoint gene-based signatures for breeds predisposed to bone cancer. These genetic tests will theoretically aid in choosing treatment plans as well as understanding the prognosis for these predisposed patients.[2] Along with genetic predisposition, males tend to be overrepresented with an increased risk of 20-50%.[1,2,6] A majority of patients are diagnosed between the ages of 7 and 9 years;[6] however, there is a bimodal age distribution with a smaller subset of the population diagnosed between 18 and 24 months of age.[7]

Osteosarcomas are mesenchymal in origin, meaning they arise from connective tissue in the body. Mesenchymal tumors tend to spread hematogenously, with the lungs being the primary site of metastasis.[5] In canines, osteosarcomas typically arise in the appendicular skeletal system with 98% of tumors occurring along the metaphysis of long bones.[6] Common sites include the proximal humerus, distal radius, distal femur, and proximal tibia (“away from the elbow, toward the knee").[2] Metaphyseal areas are thought to be primarily involved because they are especially active during skeletal development and are also weight-bearing areas of the bone.[3]

While not completely understood, other potential causes of osteosarcomas include metal implants and chronic osteomyelitis.[5] Osteosarcomas usually arise due to increased osteoblastic activity in the medullary cavity which then penetrates the cortex and extends into the subperiosteum causing the formation of a large, painful mass. Osteosarcomas often have a radiographic sunburst appearance which is the result of tumor expansion, mineralization, and formation of periosteal spicules invading the surrounding tissue. The swelling that accompanies osteosarcomas is due to fibroblasts that infiltrate the surrounding tissue and cause decreased circulation.[3] Extensive breakdown of the normal structure of healthy bone coupled with continued use of the affected limb commonly leads to pathologic fractures in the tumor area.

DIAGNOSTIC APPROACH/CONSIDERATIONS

A full diagnostic panel should be performed on patients with suspect osteosarcoma, including a complete blood count, serum chemistry panel, and urinalysis to determine if underlying disease processes are present. In patients with osteosarcoma, bloodwork can be normal. One abnormality that may be present is elevation of alkaline phosphatase (ALP). ALP has both liver and bone isoenzymes, and in patients with osteosarcoma, malignant osteolysis causes a release of this enzyme into the blood.

Radiographs of ulnar osteosarcomas show changes consistent with a primary bone tumor present most commonly at the distal third of the ulna.[1] These primary bone tumors usually have permeative and/or moth eaten lysis, severe cortical destruction, and irregular periosteal new bone production. The periosteal new bone invading surrounding tissues can create the sunburst appearance discussed above, but it can also have a variable appearance on radiographs. These characteristics, along with a long zone of transition from normal to abnormal bone and significant soft tissue swelling, lead to the diagnosis of an aggressive primary bone tumor. The presence of Codman's triangle is also a common finding, as the tumor causes destruction of the bone and periosteal elevation as it expands.[3] Interestingly, osteosarcomas rarely cross joint spaces, but both orthogonal and oblique views of the affected limb should be utilized to definitively identify which bones are involved.[2] Discontinuity of the bone cortex around the tumor is not an uncommon finding and would indicate a pathologic fracture.

Several imaging modalities should be utilized for diagnosis of metastasis as well as staging in patients with osteosarcoma. Because these mesenchymal tumors spread via the bloodstream, it is important to obtain radiographs of the thorax and abdomen to rule out the presence of gross metastasis. Metastasis at the time of diagnosis greatly affects not only the prognosis for the patient, but also the patient's course of treatment. Therefore, close attention should be given to the lungs; however, thoracic radiographs that are negative for obvious metastasis do not rule out spread of disease as this is not a sensitive diagnostic tool. Computed tomography (CT) of the thorax is a much more sensitive diagnostic tool for the presence of pulmonary metastasis. CT provides higher spatial contrast resolution as well as the absence of superimposition of surrounding structures; therefore, it should be presented to the client as an option to better understand the patient's disease progression.[8] Magnetic resonance imaging (MRI) is the diagnostic tool most helpful in surgical planning as it reveals the most accurate amount of intramedullary involvement of affected bones.[9] Ultrasound of the tumor can also be helpful. While ultrasound may not reveal any new information, it is useful for ultrasound-guided fine needle aspiration of the tumor for the collection of cells.

One of the most effective tools practitioners should have in their arsenal is the use of fine needle aspiration (FNA). FNA is a fast, inexpensive, and safe way to diagnose osteosarcoma. Obtaining samples requires limited resources, and slides can be quickly stained and read in-hospital. There is minimal morbidity associated with the procedure as it requires only a small needle that can collect cells without compromising surgical margins.[10] Cytology often shows neoplastic osteoid production, with spindled to round and polygonal-shaped neoplastic cells with abnormally placed cytoplasm.[1] FNA has been shown to be nearly 95% accurate and 91% sensitive in diagnosing osteosarcoma, especially when considering patient presentation and imaging. While there are many advantages to this diagnostic method, one limitation is difficulty distinguishing matrix subtypes (collagen, osteoid, chondroid, hyaline, telangiectatic); however, as each subtype is treated in a similar manner, it is diagnostic for osteosarcoma and does not affect treatment of the tumor.[10]

Histopathology yields a definitive diagnosis of osteosarcoma and can differentiate between osteoblastic, chondroblastic, fibroblastic and other forms of the tumor.[2] Histopathology is generally obtained after surgical removal of the tumor. Tissue biopsies taken prior to surgery increase the incidence of pathologic fractures, as it takes tissue from the center of already compromised bone.[5]

TREATMENT AND MANAGEMENT OPTIONS

While the prognosis is guarded, treatment can provide pain relief and possibly extend the survival time of patients. The ultimate goal of treating osteosarcomas is local control of macroscopic tumor through surgery and/or radiation therapy followed by control of metastasis and microscopic cancer through the use of chemotherapy.

Surgery is the first step in treating these patients as it eliminates presence of the painful tumor. With most cases of osteosarcoma, amputation of the affected limb is indicated. While amputation rids the patient of the primary problem and patients typically respond well, there is a recovery period where their mobility is compromised while adjusting to walking on three legs. With ulnar osteosarcomas, a different approach can be made. Limb-sparing procedures such as ulnar ostectomies can provide the patient with almost immediate pain relief,[1] and should be considered if the patient has a neurological or orthopedic disease affecting other limbs, which are contraindications for amputation.[6] Limb-sparing procedures have the ultimate goal of preserving function of the affected limb, and many options are available for such a procedure depending on the location of the tumor.[11] Osteosarcomas of the front leg tend to be better candidates for salvage procedures than tumors affecting the hind limbs[12] since salvage procedures often involve arthrodesis or fusing of surrounding joints. Arthrodesis of joints of the hind limb does not allow the patient proper mobility and often result in high rate of infection.[13]

Local recurrence of osteosarcomas is hindered if the affected limb is treated pre-operatively with chemotherapeutic drugs and radiation. This attempt to eliminate tumor cells pre-operatively also aids in removal of the tumor during surgery.[12] Prior to surgery, radiographs should be used to confirm that less than half of the bone is compromised. Ideally, candidates for limb-sparing procedures would have less than 360 degrees of soft tissue involvement surrounding the tumor as healthy soft tissue is needed for proper healing of the surgical site.[13] Pathologic fractures would make these procedures contraindicated due to the high likelihood that tumor cells have seeded into surrounding tissues, and should be ruled out prior to surgery.[11] As mentioned above, advanced imaging such as CT and MRI is helpful in locating metastasis as well as planning for surgery. MRI images highlight intramedullary tumor cells and display the image in multiple planes, allowing surgeons to properly measure tumor margins. It is important to obtain these images and measurements prior to beginning chemotherapy, as chemotherapeutic drugs lead to cell death and hemorrhage of the area and compromise the accuracy of the images.[9]

Tumors compromising weight-bearing bones such as the radius and tibia should be removed with 3-5 cm margins, resulting in a large defect in the bone. Most commonly, this defect is filled with a cortical allograft (cortical bone harvested from another canine patient) that is mixed with polymethylmethacrylate. Other methods include prosthetic placement, bone distraction osteogenesis that slowly fills in the defect, sterilization of the bone via pasteurization, autoclaving, or intraoperative irradiation, and replacement of the affected bone with healthy bone such as with the ulna rollover and manus translation techniques.[11] Tumors affecting non-weight-bearing bones require procedures such as partial ulnar ostectomies and do not require allografts or bone plates for stabilization.[12] With each method, soft tissue reconstruction around the excised tumor is indicated.[11]

Not surprisingly, shorter recovery time is seen with limb-sparing procedures, and the patient is able to return to function more quickly when only the affected portion of the bone is removed instead of the entire limb. Complications seen with partial ulnar ostectomies include radial fractures and surgical site infections. Radial fractures can occur if the radial cortex is disrupted during the ulnar ostectomy due to accidental manipulation or the placement of a cortical screw in attempt to stabilize the leg.[1] Post-surgical infection at the surgery site is common with limb-sparing procedures. Interestingly, several studies have shown that animals that acquired a surgical site infection that was properly treated with antibiotics had an increased survival time.[6] Theoretically, this is secondary to activation of the anti-tumor immune system as a bystander effect of the response to the infection.[2]

Radiation therapy in combination with limb-sparing surgeries can help to control local recurrence of osteosarcoma but also has the added benefit of helping to alleviate patient discomfort by decreasing pain and inflammation. The type of surgery performed on these patients (limb sparing vs. amputation), does not affect survival times. Ninety percent of patients who undergo surgery as the sole means of treatment will still develop metastasis. The most important aspect for extending survival is the addition of chemotherapy, with standard of care being surgery followed by chemotherapy.[6] The drug choice for chemotherapy does not seem to have an instrumental effect on survival time, and the chemotherapy regiment should be tailored to each patient with consideration given to quality of life for both the patient and the owner, toxicity to the patient, and goal of therapy.[2] The use of carboplatin has shown to help increase patient survival rates with average survival time being 320 days. Forty-eight percent of patients treated with carboplatin survive to one year, and 18% survive to two years past initial diagnosis.[5] Chemotherapy implemented after the development of metastasis has not been effective in prolonging patient survival times, nor has pulmonary metastacetomy along with radiation over one year from the time of diagnosis.[6]

EXPECTED OUTCOME AND PROGNOSIS

Due to its aggressive behavior, osteosarcomas carry a guarded to grave prognosis. Mean survival time (MST) without treatment is only 2.6 months in dogs with osteosarcoma. With treatment, MST is approximately five months, though this can be increased to one year with the addition of chemotherapy. As previously discussed, surgical site infections that were treated with antibiotics have shown to increase the survival time (~540 days) of patients who underwent limb-sparing surgeries. Limb-sparing surgeries have approximately 170 days from initial diagnosis to time of reoccurrence. One study showed that metastasis can occur approximately

323 days after initial diagnosis, and as previously discussed, the primary site of metastasis is the lungs. If the animal survives one year past the initial diagnosis, mean survival time is typically an additional 8 months.[6]

Negative prognostic indicators that accompany the diagnosis include age (<5 years or >10 years), increased body weight, histologic grade of the tumor, evidence of gross metastasis or pathologic fracture at time of diagnosis, and serum alkaline phosphatase levels >110 U/L at time of diagnosis.[2,6] The prognosis is considered even worse if increased serum alkaline phosphatase does not decrease by 40 days post-surgical intervention, as this indicates malignant osteolysis occurring elsewhere in the body. Location can also affect prognosis with shorter survival times associated with osteosarcomas of the ribs, scapula, and proximal humerus. The telangiectatic subtype of osteosarcoma is highly vascular and often confused with hemangiosarcoma; it carries the worst prognosis of all subtypes of osteosarcoma with a MST of just 208 days.[1]

Staging of osteosarcomas is a useful prognostic tool, and uses the "TNMG" system (tumor, node, metastasis, and grade). Stage 1 incorporates low grade tumors without evidence of metastasis, high grade tumors without metastasis are Stage 2, and Stage 3 includes animals that have obvious metastasis. The subcategory of "a" indicates intramedullary lesions, and the subcategory "b" indicates extramedullary lesions. Canine patients are typically diagnosed as Stage 2b at time of presentation.[2]

OTHER PERTINENT INFORMATION

The phenomenon of post-operative infections leading to better survival times for patients was observed as early as 1890 when William Conley observed that inoculation of *Streptococcus pyogenes* lead to the regression of certain cancers. This phenomenon has significant implications today, as a recent study found that dogs diagnosed with osteosarcoma that experience post-operative infections have increased metastasis-free intervals and are 25 times less likely to die due to osteosarcoma. While not completely understood, this is likely due to non-specific stimulation of the immune system that also activates the body's anti-tumor response. The anti-tumor response involves cells such as tumor-associated macrophages, natural killer cells, and monocytes. These cells are all a part of the innate immune system, and these findings indicate that osteosarcomas are immunogenic.[7]

The fact that osteosarcomas are immunogenic has huge implications for future control of microscopic metastasis, which is undoubtedly present by the time our canine patients present with a macroscopic tumor. Vaccinations such as Bacillus Calmette-Guerin (BCG), a vaccine against tuberculosis, have been studied since the 1920's when it was found that human patients with tuberculosis had a decreased frequency of cancer. Studies in the 1970's showed longer metastasis-free intervals and thus longer survival times in canine patients that were given intravenous BCG after being diagnosed with osteosarcoma. More recently, vaccines against *Listeria monocytogenes* have been used to delay the progression of osteosarcoma. The implications of these vaccines in cancer patients, as well as their widespread use, is still being studied but show promising possibilities for the use of vaccines to help in the treatment of human and canine osteosarcoma.[7]

CONCLUSION

In summary, osteosarcoma is the most common primary bone tumor seen in canine patients with 10,000 dogs diagnosed each year in the United States.[7] There are several options for diagnosis of this bone cancer, with fine needle aspirate of the tumor being a fast and simple way to obtain a diagnosis. While ulnar osteosarcomas are comparatively rare, limb-sparing procedures can be utilized as opposed to amputation. Though these two surgeries do not carry different prognoses, limb-sparing procedures rapidly eliminate pain and allow the patient to return to function more quickly. Standard of care of any dog with osteosarcoma includes surgery to eliminate macroscopic evidence of the tumor followed by chemotherapy. It is important for the practitioner to follow up and closely monitor patients with osteosarcomas because of the aggressive behavior of these tumors and their tendency to return. While still under investigation, the use of vaccines to help eliminate microscopic tumor metastasis is a promising future treatment option for both human and canine osteosarcoma.

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