A CYST BY ANY OTHER NAME

Rachel K. Holman

Mississippi State University

College of Veterinary Medicine

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Adviser:

Hayley Gallaher, DVM, MS, Practice Limited to Surgery

Introduction

Within the bone marrow, there are three categories of cells:[1] hematopoietic cells (which develop into all types of blood cells), endothelial cells (which govern tissue development and regeneration using signaling molecules), and stromal cells. The stromal cells are non-hematopoietic cells of mesenchymal origin consisting mainly of fibroblast-like features.[2] These stromal cells commonly differentiate into bone, cartilage, adipocytes, and hematopoietic supporting tissues[3] but also have the potential to differentiate into muscle, neural tissue elements, and hepatocytes.[4,5] In normal bone, these stromal cells, also referred to as mesenchymal stem cells, are within the cambium layer of the periosteum as well as the fatty marrow in the medullary cavity. In mammals, the stromal cells help with bone callus formation in fracture healing[6] and manipulation of these cells have utility in bone grafting and orthopedic surgery for various orthopedic conditions including non-unions, mal-unions, bone cysts, various bone defects, and Legg-Calvè-Perthés disease.[7] Additionally, mesenchymal stem cells are used for therapies in regeneration and repair of cartilage, muscle, tendon, and ligament.[8]

Tumors arising from bone are classified based on the predominant matrix and cell differentiation present. The most common primary bone tumors arise from mesenchymal precursors, which are associated with bone, connective tissue, adipocytes, blood vessels, and the hematopoietic cells of bone marrow.[9] These mesenchymal elements can undergo neoplastic transformation and differentiate into sarcomas within the bone or medullary cavity. Thus, the mesenchymal cells – also referred to as bone marrow stromal cells – are the source of all primary medullary bone tumors in dogs: osteosarcoma, chondrosarcoma, fibrosarcoma, hemangiosarcoma, and liposarcoma.[10]

There are rare instances in which these neoplasms do not fully differentiate into a specific tumor type, and represent poorly differentiated mesenchymal tumors, first recognized in humans by Lichtenstein and Bernstein.[11] These tumors are histologically characterized by a transition between undifferentiated mesenchymal, or stromal cells, and various differentiated osseous or chondroid components.[12] In 2004, Daugaard[13] reclassified various types of soft tissue sarcomas based on immunohistochemistry of pathologic material and changes in oncological nomenclature. One such reclassification was given to tumors previously described as 'pleomorphic/giant cell/inflammatory malignant fibrous histiocytomas,' which were subsequently termed 'undifferentiated pleomorphic sarcomas.' Based on the 2013 WHO Classification of Tumors of Soft Tissue and Bone, this diagnosis is one of exclusion as it represents tumors which cannot be classified into any other category due to lack of cell line differentiation or lack of distinguishing histologic or immunohistochemical features.[14]

Due to this recent change in classification, there are limited case reports concerning this group of tumors, and little is known about their behavior, metastatic rate, appropriate treatment, or prognosis. In humans, these tumors are rare, accounting for 2% to 5% of all primary malignant bone neoplasms and are reportedly more common in older males.[15] Current standard of care based on human protocols is neoadjuvant chemotherapy prior to wide surgical excision.[14] Doyle also suggests these tumors have a metastatic rate of at least 50%.[14] Prognosis in veterinary medicine is not currently reported, though a major prognostic indicator in humans is degree of tumor necrosis following chemotherapy.[16]

History and Presentation

Romeo, an 8 year old male neutered Rottweiler, presented to Mississippi State University College of Veterinary Medicine on August 21, 2018 for referral of acute, intermittent lameness

in the left hind limb of approximately three weeks duration. Romeo originally presented to his primary veterinarian on July 27, 2018 for acute onset lameness in his left hind limb. Radiographs at the primary veterinarian revealed a bone lesion, suspected to be a bone cyst, on the distal tibia of the left hind limb. Romeo was prescribed an analgesic for two days as well as strict rest for three to five days. Romeo's owners report his lameness seemed to resolve after approximately three days, and they resumed his normal activity level. Romeo's lameness returned the following week, and thoracic radiographs were taken with no evidence of pulmonary nodular metastasis noted within the thoracic cavity. Romeo was then referred to MSU-CVM Surgery Service for consultation of the suspected bone cyst.

On presentation, Romeo was bright, alert, and responsive. He weighed 36.5 kilograms with a body condition score of 5/9 (ideal body condition). His vital parameters were within normal limits (temperature: 101.3°F, heart rate: 140 beats per minute, and panting respiration). His mucous membranes were pink and moist, with a capillary refill time of less than two seconds. Cardiopulmonary auscultation, abdominal palpation, and palpation of peripheral lymph nodes were all within normal limits. On orthopedic exam, Romeo was non-painful on palpation of all limbs, including the left hind limb, and he had a negative cranial drawer and tibial thrust on both hind limbs. There was mild soft tissue swelling on the left distal tibia, as well as moderate muscle atrophy of the left hind limb. Romeo given a grade two out of five lameness score since he was also off-loading weight from the left hind limb onto the right hind limb at both a stand and a walk.

Diagnostic Approach/Considerations

Radiographs of the left and right tibia/fibula, left and right radius/ulna, and left and right humerus were obtained as part of the initial diagnostic work-up. In addition to radiographs, a

serum chemistry panel, complete blood count, and urinalysis were obtained, all of which showed no significant abnormalities. The radiographs of the right tibia/fibula, left and right radius/ulna, and left and right humerus showed no evidence of bony lesions, other than mild osteoarthritis of various joints (including right and left glenohumeral joints, and right cubital joint).

The radiographs of the left tibia confirmed the presence of an expansile, smoothly marginated region of geographic lysis within the distal tibial diaphysis and metaphysis, as found by the primary veterinarian. The cortices surrounding the region of the lesion remained intact and of normal thickness, though the cortices within the expansile region were thin. There was also mild periarticular osteophyte formation on the lateral malleolus. These radiographs depicted a monostotic, non-aggressive lesion, and so a presumptive diagnosis of a bone cyst was made. An aneurysmal bone cyst, neoplasia (primary or metastatic), and fungal osteomyelitis were considered less likely given the non-aggressive characteristics of the lesion.

A fine needle aspirate was taken of the lesion, which showed large amounts of blood, along with low numbers of round to oval, large mesenchymal cells with mild anisocytosis and anisokaryosis. A definitive diagnosis could not be obtained via cytology due to low cellularity; however mild atypia indicated the need for histopathology due to the inconsistency with the radiographic interpretation.

Treatment and Management

With the tentative diagnosis of a bone cyst made, Romeo's treatment plan included curettage of the bone cyst in the left tibia, as well as an autologous cancellous bone graft taken from the left proximal humerus. On August 22, 2018, Romeo was anesthetized and prepped for surgery. An approximately three centimeter incision was made over the left distal tibia just above the tarsus, and an approximately three millimeter wide foramen through the dorsal cortex of the

tibia was made using a Jacob's chuck. Fluid within the lesion was drained and the soft tissue lining within the lesion was debrided and submitted for histopathology. An autologous cancellous bone graft from the greater trochanter of the left proximal humerus was packed into the lesion in the distal tibia. The left hind limb was bandaged and stabilized with a lateral splint. Romeo recovered from surgery uneventfully. Romeo was hospitalized overnight in the intensive care unit and was prescribed Tylenol 4 (acetaminophen + codeine at 1.6mg/kg orally every 8 hours) and carprofen (2mg/kg orally every 12 hours), and remained comfortable. He was discharged the following day, at which time he was placing weight on his left hind limb and walking with the assistance of a sling.

Histopathology of the lining of the suspected bone cyst revealed a pleomorphic infiltrate of mesenchymal cells (both spindle-shaped and polygonal) with moderate anisokaryosis and anisocytosis. Aggregates of these cells formed minute deposits of hyalinized collagenous matrix resembling the osteoid; however, the cells lacked the angular profiles of osteogenic mesenchyme. At high powered fields, up to two mitotic figures per field, and pleomorphism were present. These findings were consistent with a highly malignant undifferentiated pleomorphic sarcoma of bone marrow stromal cell origin.

Additional interpretation of the radiographs of Romeo's left tibia was conducted due to the histopathological findings of a highly aggressive lesion, and further evidence of malignancy was noted. There was hyperdense medullary bone present at the caudal cortex proximal to the lesion, suggestive of dystrophic mineralization, which was attributed to a probable infarct in that area. A lytic, poorly demarcated area in the medullary cavity proximal to the arch formed by the proximal rim of the cystic lesion was also noted. These two important findings would not have been present in a non-aggressive bony lesion, such as a bone cyst,[17] thus supporting the

histopathological diagnosis of a highly malignant undifferentiated pleomorphic sarcoma of bone marrow stromal cell origin.

Pathophysiology

Undifferentiated pleomorphic sarcomas (UPS), previously termed malignant fibrous histiocytoma,[13] have caused much conflict within the field of veterinary and human oncology. The majority of research of this topic has been in human medicine, and thus has been extrapolated to veterinary medicine. In human medicine, debate still exists about what cell type serves as the origin for this type of tumor with histiocytes, fibroblasts, or cells with intermediate features of both all having been proposed. More recently, a primitive pluripotent mesenchymal stem cell with both histiocytic and fibroblastic potential has also been suggested.[18] The current hypothesis now proposes these undifferentiated pleomorphic sarcomas are viewed as a common morphologic pattern shared by various pleomorphic neoplasms regardless of their differentiation.[18] Another related hypothesis is that these tumors represent a "final common pathway" for tumor growth since tumors can lose their differentiation pattern as they grow and thus ultimately reach this undifferentiated pattern seen in these UPS.[18] Thus, the nomenclature surrounding this diagnosis is quite convoluted, which makes researching its behavior and prognosis difficult.

In human medicine, multiple hypotheses have been put forth regarding predisposing factors for undifferentiated pleomorphic sarcomas of bone. Some studies have shown these tumors arise secondary to various musculoskeletal disorders including chronic osteomyelitis,[19] bone infarcation, fibrous dysplasia, osteitis deformans, and enchondroma[20] – all of which are exceedingly rare in veterinary medicine. Currently, there is a lack of evidence supporting that these pre-existing conditions also predispose dogs, and other small animals, to this tumor.

Regardless of the cause or suspected predisposing factors, UPS does show similar clinical features in humans. UPS is most commonly a high grade sarcoma affecting mainly the long bones such as femur, humerus, tibia, and ulna,[15] though it has also been reported in other bones in the trunk and skull. One retrospective study found the knee was the most common site of occurrence.[21] There are also similar features in the signalment of the human patients diagnosed with undifferentiated pleomorphic sarcoma; it most commonly affects older males.[15] U

Undifferentiated pleomorphic sarcomas have been reported in small animals with the majority of cases in dogs being found in the spleen,[22] but other cases have been reported in the subcutis of the trunk or hindlimbs, as well as being associated with the skull.[23] Based on multiple case reports of malignant fibrous histiocytoma (the previous term used to describe undifferentiated pleomorphic sarcomas), dogs with this tumor are typically middle aged to older, with flat-coated retrievers,[24] Rottweilers, and golden retrievers being over represented.[23] Currently, there is a debate on whether or not a sex predilection exists for this type of tumor. Prognosis and treatment is also a subject of much debate, especially in veterinary medicine; however, there is consensus that histologic subtype of UPS contributes significantly to the overall prognosis. In humans, UPS of giant cell variation seems to carry a worse prognosis based on local behavior, high rate of metastasis to multiple organs, and low short term survival of patients.[15] The few case reports described in dogs report these tumors as being highly metastatic (especially to the lungs, liver, lymph nodes, and subcutaneous tissue),[23] locally aggressive with high local recurrence even after wide surgical excision,[25] and a median survival time of only sixty one days without treatment.[26] Current treatment protocols, which are extrapolated from human medicine, include surgical resection, intraoperative radiotherapy, and chemotherapy (either pre- or post-operatively). One retrospective study looking at ten cases of malignant

fibrous histiocytomas of giant cell variant claims a median survival time of 161 days with one or more of the appropriate treatment protocols.[26] There are significantly fewer studies and case reports describing UPS with an unidentified histologic subtype, so behavior, treatment options, and prognosis is currently unknown.

Case Outcome

Due to the relatively unknown prognosis of Romeo's diagnosed tumor type, efforts were made to have him brought back to MSU-CVM Surgery Service for a left hind limb amputation, since wide surgical excision is the treatment of choice for other malignant tumors of bone. Tumor staging, including repeat thoracic radiographs, and abdominal ultrasound, would have also been pursued to determine if metastasis had occurred. However, Romeo re-presented to his primary veterinarian with recurrent lameness in the left hind limb approximately twenty two days after surgery, at which time the owners elected humane euthanasia without necropsy. Since a necropsy was not performed, the extent of damage and other tissue samples could not be examined to further investigate this particular tumor.

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