Spontaneous regression of osteosarcoma in four dogs

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- Spontaneous regression of primary bone tumors is rare but has been reported in the human literature.
- Determination of spontaneous regression of a bone tumor is based on partial or complete disappearance of a tumor in the absence of treatment or presence of inadequate treatment.

A 9-year-old castrated male Irish Setter weighing 96.8 lb (44 kg) was evaluated because of progressive left forelimb lameness of 6 weeks' duration. On physical examination, a firm swelling was evident in the distal portion of the radius and the carpal region. A CBC, biochemical analysis, and urinalysis were performed at that time, and results were unremarkable, with the exception of a mild increase in alkaline phosphatase activity (175 U/L; reference range, 18 to 141 U/L). Radiography was performed and revealed a combined destructive and proliferative lesion within the distal metaphysis of the radius. A specimen of the radial lesion was obtained via Jamshidi needle biopsy and examined histologically. The lesion was diagnosed as spindle cell sarcoma, possibly spindle cell osteogenic sarcoma. However, there was concern regarding the possibility of osteochondroma with associated distortion of adjacent bone and exuberant reactive fibroplasia. The dog was treated with carprofen (2.2 mg/kg [1.0 mg/lb] of body weight, PO, q 12 h) and referred to a specialty practice to obtain additional biopsy specimens.

Three weeks later, additional needle core biopsies were obtained from the distal portion of the left radius, and osteosarcoma was confirmed histologically. At that time the dog was referred to the Colorado State University Veterinary Teaching Hospital for further evaluation and possible limb-sparing treatment.

At initial evaluation, the dog was icteric. A CBC and serum biochemical analysis were performed. Hematologic examination indicated neutrophilic leukocytosis (17,200 cells/µl; reference range, 6.0 to 17.0 × 10^3 cells/µl). Serum biochemical analysis revealed mild hyponatremia (144 mg/dl; reference range, 145 to 158 mg/dl); decreased BUN (4 mg/dl; reference range, 7 to 28 mg/dl); hypercholesterolemia (1,125 mg/dl; reference range, 130 to 300 mg/dl); hyperbilirubinemia (7.6 mg/dl; reference range, 0 to 0.4 mg/dl); and increased alanine aminotransferase (1936 U/L; reference range, 10 to 120 U/L), aspartate aminotransaminase (201 U/L; reference range, 16 to 40 U/L), alkaline phosphatase (4,743 U/L; reference range, 8 to 141 U/L), and γ-glutamyl transpeptidase (107 U/L; reference range, 0 to 6 U/L) activities. A coagulation profile was performed prior to laparoscopy to obtain biopsy samples of the liver. Buccal mucosal bleeding time, activated partial thromboplastin time, and 1-stage prothrombin time were within reference ranges. Ultrasonography of the abdomen revealed a small hypoechoic nodule (8 × 13 mm) within the midportion of the liver, and the remaining liver parenchyma appeared normal. On ultrasonographic examination, echogenic material was identified within the lumen of the gallbladder; there was no evidence of extrahepatic obstruction. Biopsy specimens of the liver were obtained laparoscopically. A histologic diagnosis of chronic active pericholangitis and cholestasis was made; neoplastic cells and infectious organisms were not seen. Biopsy specimens were submitted for anaerobic and aerobic culture with susceptibility; microorganisms were not grown.

Initial treatments included enrofloxicin (5 mg/kg [2.3 mg/lb], PO, once daily), amoxicillin (22 mg/kg [10 mg/lb], PO, q 12 h), and ursodeoxycholic acid (15 mg/kg [6.8 mg/lb], PO, once daily) to increase bile acid flow. Survey radiography of the vertebral column, abdomen, and left radius and ulna was performed. Radiography of the abdomen and vertebral column did not reveal any abnormalities; radiography of the left radius and ulna revealed a combined destructive and proliferative lesion within the distal aspect of the radius. Thoracic radiography did not reveal evidence of pulmonary metastatic disease. A whole body bone scan was performed with 12.8 mCi of technetium Tc 99m-labeled albumin hydroxydiphosphonate injected IV. Intense uptake in the left distal portion of the radius was seen, which was highly supportive of a neoplastic condition.

Because of the severity of hepatic disease, surgical treatment of the radial osteosarcoma was not recommended. At that time, it was believed that the liver disease would likely be more fatal to the dog than the primary bone tumor. The dog was discharged with a grave prognosis and instructions to the owner to discontinue carprofen because of the potential hepatotoxic effects[1] and continue on antibiotics, vitamin E, and ursodeoxycholic acid treatment for 6 weeks, with a recheck examination with the dog's veterinarian for continued

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care. Two years later, the dog returned to the referring veterinarian for a follow-up examination. Radiography of the left radius was repeated and revealed considerable resolution of the previous biopsy-confirmed osteosarcoma. The owners reported the dog was free of clinical signs of disease and had no signs of lameness.

A 13-month-old female spayed mixed-breed dog weighing 90.2 lb (41 kg) was evaluated by the referring veterinarian because of a 2-week history of right hind limb lameness. At that time, radiography of the right hind limb was performed and revealed a lytic lesion in the proximal portion of the tibia (**Fig 1**). The following day, a Jamshidi needle biopsy was performed through a caudolateral skin incision over the center of the mass. Histologic examination of the mass confirmed the lesion to be a high grade osteosarcoma (**Fig 2**). The owners declined treatment, and the dog was discharged with instructions to the owner to administer carprofen (2.2 mg/kg [1.0 mg/lb], PO, q 12 h) for 10 days. Additional medications administered by the owner included ubiquinol-10[a] (10 mg, PO, daily). Nine months later, the dog was reevaluated and, with the exception of mild muscle atrophy in the right hind limb, was clinically normal. There was no swelling or signs of pain in the area of the prior mass. Radiography of the right hind limb revealed almost complete resolution of the lytic process with a smooth sclerotic periosteal reaction at the site (**Fig 3**).

A 5-year-old male castrated Golden Retriever

Figure 1—Dorsoventral radiographic view of the right tibia of a dog. Notice the lytic lesion of the proximal portion of the tibia (arrow), which is highly suggestive of a primary bone tumor.

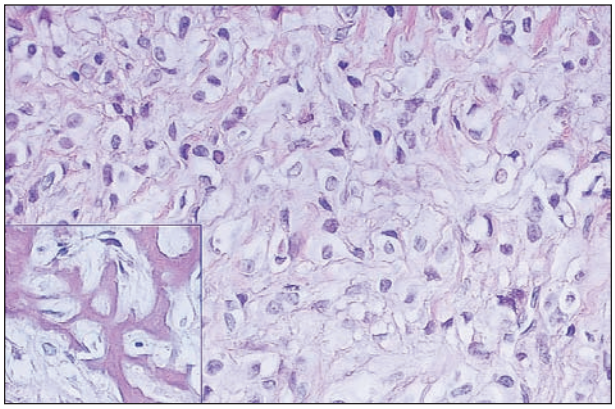

Figure 2—Photomicrograph of a histologic section of the tumor obtained from the dog in Figure 1. Notice the polygonal to spindloid cells with pleomorphic oval nuclei and occasional mitotic figures, typical for osteosarcoma. Inset—tumor bone matrix with cells within lacunae, which is diagnostic for osteosarcoma.

Figure 3—Dorsoventral radiographic view of the right tibial lesion from the dog in Figure 1, obtained 9 months later (radiographic views in the same orientation not available). Notice there is considerable resolution of the previous lytic lesion with a smooth sclerotic periosteal reaction at the site.

weighing 83.6 lb (38 kg) was evaluated by the referring veterinarian for a right forelimb lameness of 2 weeks' duration. On physical examination, the dog had signs of pain on extension and flexion of the right carpus. Radiography of the right and left carpi was performed. A lytic lesion and loss of normal trabecular architecture were detected in the distal portion of the right radius. The dog had previously been on carprofen at a standard dose (2.2 mg/kg [1.0 mg/lb], PO, q 12 h) for mild hip dysplasia and was continued on the drug. Within 10 days, the dog became non–weight-bearing on the right forelimb, and needle core biopsy specimens of the mass were obtained. Histologic evaluation of the biopsy samples confirmed a diagnosis of osteosarcoma. The owners declined further treatment, and the dog was discharged with instructions to the owner to restrict its activity, continue carprofen, and return for euthanasia if the dog's quality of life was declining. Within the following week, the owners reported the dog was improving and slowly returning to a normal level of activity. One year later, the dog was reevaluated, and radiography of the right radius was repeated. Smooth sclerotic bone replaced the previous lytic lesion, and normal trabecular pattern filled the distal radius.

A 2-year-old sexually intact male Rottweiler weighing 121 lb (55 kg) was evaluated by the referring veterinarian because of a mass over the distal portion of the right radius that was detected by the owner. Radiography was performed and revealed a combined destructive and lytic lesion of the right radius. At that time, needle core biopsy specimens were obtained and sent for histologic evaluation. A diagnosis of a high-grade osteosarcoma was made. The owner declined all recommended treatment options and elected to begin alterative therapies. The dog did not receive **nonsteroidal anti-inflammatory drugs (NSAID)** or pain medications. Nine months later the mass had decreased substantially; radiography revealed considerable resolution of the previous lesion.

Spontaneous regression of malignant primary bone tumors is rare, but it has been reported in the human literature.[2-9] Although spontaneous regression of primary bone tumors has not been documented in dogs or cats, spontaneous regression of presumed pulmonary metastases from a tibial fibrosarcoma in a dog and spontaneous regression of lymphoma in a cow have been reported.[10,11] Spontaneous resolution of a possible primary bone tumor in a dog was reported in a letter, although the diagnosis was not confirmed by biopsy.[12] To the authors' knowledge, there are no reports in the veterinary literature of a biopsy-confirmed malignant primary bone tumor with spontaneous regression.

Osteosarcoma is the most common primary bone neoplasm of dogs, and it has been estimated that 8,000 new cases occur each year in the United States.[13] If left untreated, mean survival time is reported to be 107 days.[b] In the 4 dogs of this report, a diagnosis of osteosarcoma was confirmed histologically; all biopsy samples had been reviewed by a single pathologist (BEP). These 4 dogs with primary osteosarcoma were followed for 6 and 9 months and 1 and 2 years, respectively, at which time each dog was alive, free of clinical signs of disease, and had substantial resolution of the previous masses on radiologic follow-up examinations.

Diagnosis of a primary malignant bone tumor is often suggested by radiographic findings alone; however, histologic evaluation of a biopsy sample is needed to confirm the diagnosis. Obtaining and evaluating a biopsy sample is necessary to differentiate among radiographic bone lesions such as malignant primary bone tumors, benign bone tumors, tumors arising from marrow elements, metastatic tumors, osteomyelitis, fractures, and degenerative lesions.[14] In dogs, performing a closed biopsy with a needle core has an diagnostic accuracy rate of 91.9% with a specificity of 100% for the diagnosis of osteosarcoma.[14,15] Biopsy remains the definitive diagnostic procedure for bone lesions; the Jamshidi procedure was used in 4 dogs of our report because of the ease of the procedure and high accuracy rate.

There are several proposed mechanisms for spontaneous regression of tumors; the most cited cause is immunologic. Early studies in humans revealed that transplanted tumors usually regressed, suggesting that the immune system responded to tumors. Other studies have indicated that immunosuppressed patients have a higher incidence of tumors. It is believed that the immune system may prevent the development of some tumors through early destruction of abnormal cells.[16] The resemblance of these proposed model systems to naturally occurring tumors and immune system response is unknown.

Three of the 4 dogs in our report received the NSAID carprofen, which is antipyretic and analgesic in dogs. Nonsteroidal anti-inflammatory drugs have been proposed to inhibit the growth of some tumors by inducing cell death (apoptosis), inhibiting the **cyclooxygenases (COX-1** and **COX-2)**, inhibiting prostaglandin synthesis, or causing an increase in production of the prostaglandin precursor arachidonic acid.[17] It is thought that the proposed antitumor mechanisms occur through the inhibition of COX-2 and prostaglandin synthesis. There is evidence that downregulation of COX-1 and COX-2 prevents formation of prostaglandins, which have multiple effects favoring tumorigenesis. Several studies support the theory that inhibitors of COX-1 and COX-2, and thereby prostaglandin formation, protect against colon, mammary, esophageal, lung, and oral cancer in domestic animals and humans.[18] The role that carprofen may have played in the dogs of this report is unknown, and the potential antitumor mechanism of carprofen remains unsolved. Carprofen is still not considered an appropriate treatment to prolong survival time in dogs with osteosarcoma.

Osteosarcoma in dogs shares many similarities with osteosarcoma in humans: male predilection, large patient size, common sites of metastasis, and percentage of tumors with aneuploidy and high grade histologic features.[13] Osteosarcoma is the most common primary bone tumor in humans; in dogs, the incidence of osteosarcoma is 40 to 50 times greater than that in humans.[13] It is possible that osteosarcoma in these species shares a similar pathway in spontaneous regression. Further study of spontaneous regression of

osteosarcoma in dogs should be useful in understanding the process in humans and may lead to the development of immunotherapy for cancer.

[a]Coenzyme Q10, The Vitamin Shoppe, North Bergen, NJ.

[b]Zachos TA, Chiaramonte D, DiResta GR, et al. Canine osteosarcoma: treatment with surgery, chemotherapy and/or radiation therapy, The Animal Medical Center, 1993–1998 (abstr), in *Proceedings.* 19th Annu Vet Cancer Soc Conf 1999;12.

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