Factors associated with pathological fractures in dogs with appendicular primary bone neoplasia: 84 cases (2007–2013)

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Objective—To determine the incidence of pathological fractures associated with appendicular primary bone tumors in dogs managed medically and to identify potential risk factors at the time of radiographic diagnosis that may be associated with eventual pathological fracture.

Design—Retrospective case series.

Animals—84 dogs with primary long bone neoplasia treated medically.

Procedures—Medical records for dogs with a diagnosis of primary long bone neoplasia based on results of radiography that was confirmed subsequently at necropsy were reviewed. Owners elected medical treatment at a pain clinic. Data regarding clinical signs, diagnostic testing, pathological findings, and outcome were evaluated.

Results—84 dogs met study inclusion criteria with 85 limbs affected. Osteosarcoma was the most common tumor and was identified in 78 of 85 (91.8%) limbs. The median time from diagnosis to euthanasia was 111 days (range, 28 to 447 days). Pathological fractures were identified in 33 of 85 limbs (38%), with the femur most commonly affected, (8/14 [57.1%]), followed by the tibia (9/17 [52.9%]), humerus (10/27 [37%]), radius (5/25 [20%]), and ulna (1/2 [50%]). Logistic regression analysis indicated that tumors arising from long bones other than the radius had odds of eventual fracture 5.05 as great as the odds for tumors of the radius, and lytic tumors had odds of eventual fracture 3.22 as great as the odds for tumors that appeared blastic or mixed lytic-blastic.

Conclusions and Clinical Relevance—Results suggested that radial primary bone tumors were less likely and lytic tumors were more likely to fracture. The overall incidence of pathological fractures secondary to appendicular primary bone neoplasia in this study with patients treated by means of intensive management for bone pain was higher than previously reported. (J Am Vet Med Assoc 2015;247:917–923)

Osteosarcoma is the most common malignant bone neoplasia in dogs, occurring most commonly in the metaphyseal region of long bones of large- or giant-breed dogs.1–3 Previous studies4,5 have reported the most common locations for primary tumors as the distal aspect of the radius and proximal aspect of the humerus, with the proximal and distal aspects of the femur and the proximal and distal aspects of the tibia affected less commonly. Although limb amputation is still considered the gold standard for local management of primary bone neoplasia, concurrent osteoarthritis, neurologic disease, obesity, and large and giant breeds have been considered relative contraindications for amputation.4 Current treatment options for such patients include limb-sparing techniques, radiation therapy, and palliative medical care.

Pathological fracture is a well-recognized complication of malignant bone tumors.6–11 Such fractures are thought to occur as a consequence of deterioration of the viscoelastic properties of the affected bone, which predisposes to increased plastic deformation and subsequent fracture.12 As a result, the fractures usually develop spontaneously or with minimal trauma.13

In human patients, pathological fractures occur most often secondary to metastatic bone lesions because of the high incidence of bone metastasis with cancers such as prostatic and mammary carcinoma.14 The incidence of pathological fractures in individuals affected with osteosarcoma either at diagnosis or during preoperative treatment is between 5% and 10%.15,16 Previous studies have evaluated multiple factors that may be predictive of risk of pathological fracture including increased pain, lesion size of > 25 mm, radiographic osteolytic appearance, proximal lesion location, a ratio of lesion width to metaphysis width > 25 mm, and pain. A major limitation of this scoring system is that, whereas the reported sensitivity was 91%, a 35% specificity resulted in many patients undergoing unnecessary procedures including aggressive internal fixation with interlocking nails.17–19 A more recent study20 advocates the use of prophylactic osteosynthesis only when the lesion is > 30 mm in length.

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In veterinary medicine, there is little in the reported literature on the incidence of pathological fractures associated with primary bone tumors, and reports are limited to small case series. A single study evaluating pathological fractures in long bones reported that they accounted for <3% of all fractures, but that >90% of these were secondary to neoplasia in a series of 368 dogs in 1987. One study of 25 dogs with osteosarcoma and appendicular pathological fractures reported that pathological fractures do not alter the prognosis for patients undergoing amputation and chemotherapy, but the study did not account for patients for which amputation is not an option. Currently there are no reported data for the incidence of or prognostic factors for pathological fractures associated with primary neoplasia in dogs.

The purpose of the study reported here was to determine the incidence of pathological fractures associated with appendicular primary bone neoplasias in dogs aggressively managed through a pain clinic and to identify potential risk factors identified at the time of radiographic diagnosis of bone cancer associated with the eventual development of pathological fracture. Our hypothesis was that lesions with axial cortical involvement >30 mm would be more prone to pathological fracture than those with axial cortical involvement ≤30 mm.

**Materials and Methods**

**Case selection criteria**—Medical records of dogs with aggressive monostotic radiographic lesions that had been prospectively followed and managed through a pain clinic at the Matthew J. Ryan Veterinary Teaching Hospital at the University of Pennsylvania from February 2007 through February 2013 were retrospectively reviewed. Dogs for which complete medical records were available and a diagnosis of primary long bone neoplasia had been made on the basis of results of radiography, and eventually confirmed with a necropsy, were included in the study. All patients had a complete necropsy performed under the supervision of a board-certified pathologist. Patients were excluded from the study if results of radiography had been suggestive of primary bone neoplasia but results of subsequent necropsy did not confirm that diagnosis or if a necropsy was not performed. Dogs were also excluded if the primary site of neoplasia affected the ilium, ischium, or scapula. Prior treatment with palliative radiation therapy was not considered an exclusion criterion.

**Medical records review**—Information regarding history, signalment, body weight at the time of diagnosis, body condition score at the time of diagnosis, physical examination findings, Canine Brief Pain Inventory pain severity and pain interference scores, results of laboratory tests (including alkaline phosphatase activity, total calcium concentration, and total phosphorus concentration), duration from initial diagnosis until death, and necropsy findings were evaluated. The diagnosis of a primary bone neoplasia for each patient was based on the presence of a solitary aggressive osseous lesion seen on radiographs with histologic confirmation of neoplasia on necropsy.

**Radiographic examination**—Lateromedial or craniocaudal extremity radiographic views were evaluated by a single board-certified radiologist (JNS). Information regarding the affected bone, location, cortical lysis, and compression surface affected by lysis were determined via evaluation of the radiographs. Measurements regarding maximal axial cortical involvement, length of the most severely affected cortex, width of the lesion including periosteal reaction, and width of the most severely affected cortex were measured separately with radiograph-viewing software, analog films, or scanned analog radiographs (Figure 1). Compression surfaces were defined as caudal (radius, humerus, and distal aspect of the femur), medial (proximal aspect of the femur), and caudomedial (tibia). The radiographic appearance was evaluated subjectively as lytic or blastic. Lysis was defined as the presence of bone disruption, particularly involving a cortex or in which focal areas of ill-defined osteolysis were present throughout a region of the bone. Blastic was defined as a majority production of new bone described as being a smooth, solid bone formation; multilayered or lamellar bone formation; spiculated, columnar bone formation; sunburst bone formation; or amorphous new bone formation. If no feature was predominant, a classification of mixed was assigned (Figure 2).

**Necropsy examination**—A full necropsy was performed under the supervision of a board-certified pathologist.
The initial medical record search identified 120 dogs with primary bone lesions. Twenty-six dogs were excluded because of the lack of histopathologic diagnosis. Four dogs were excluded because the bones that were affected included the ilium, ischium, and scapula. Six additional dogs were excluded because the initial radiographs were unavailable for review. A single dog with 2 appendicular lesions was included because the tumors affected different metaphyseal locations and had differing tumor histopathology; these were considered 2 separate primary tumors. Therefore, 84 dogs with 85 tumors met the inclusion criteria during the study period. Male dogs represented 48 of 84 (57%) case animals (45 castrated and 3 sexually intact males), and female dogs represented 36 of 84 (43%) case animals (33 spayed and 3 sexually intact females). Case animals included mixed-breed dogs (n = 20), Rottweilers (16), Labrador Retrievers (11), Golden Retrievers (10), Greyhounds (5), Great Danes (3), German Shepherd Dogs (3), and Saint Bernards (3). There were 13 other breeds represented, including 1 each of American Bulldog, American Staffordshire Terrier, Borzoi, Boxer, Bullmastiff, Cane Corso, Doberman Pinscher, English Mastiff, Giant Schnauzer, Great Pyrenees, Irish Wolfhound, Neapolitan Mastiff, and Standard Poodle. The median age of patients in the study was 8.5 years (range, 0.7 to 13 years). The median body weight was 41.1 kg (90.4 lb; range, 21 to 81.3 kg [46.2 to 178.9 lb]). On the basis of a body condition score on a scale of 1 to 5 (1 = cachectic and 5 = obese), 33 of 85 (39%) dogs were considered overweight or obese (body condition score ≥ 4) and only 6 of 85 (7%) dogs were considered thin or cachectic (body condition score ≤ 2).

The median time from diagnosis to euthanasia or death was 111 days (range, 28 to 447 days). Eighty-five limbs were affected in 84 dogs. In the dogs evaluated, tumors were located in the proximal aspect of the humerus (n = 27), distal aspect of the radius (25), proximal aspect of the femur (2), distal aspect of the femur (12), proximal aspect of the tibia (5), distal aspect of the tibia (12), and distal aspect of the ulna (2). Osteosarcoma was the most common tumor identified, with 78 of 85 (91.8%) lesions having a histopathologic diagnosis of osteosarcoma. Other tumor types found were 3 (3.5%) cases of...
Table 1—Characteristics at time of diagnosis for 84 dogs with primary bone tumors treated medically at a pain clinic and followed until the end of life.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonfracture (n = 52)</th>
<th>Fracture (n = 33)</th>
<th>Reference range</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>8</td>
<td>9</td>
<td>0.75–13</td>
<td>0.04</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>43.1</td>
<td>39.2</td>
<td>21–62.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Body condition score (scale, 1–5)</td>
<td>3</td>
<td>3</td>
<td>1–5</td>
<td>0.64</td>
</tr>
<tr>
<td>CBPI severity score</td>
<td>4.5</td>
<td>4.5</td>
<td>1–8</td>
<td>0.58</td>
</tr>
<tr>
<td>CBPI interference score</td>
<td>5.2</td>
<td>6.17</td>
<td>0.67–8.83</td>
<td>0.53</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>114.5</td>
<td>116.5</td>
<td>44–413</td>
<td>0.31</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>10.4</td>
<td>10.45</td>
<td>9–11.6</td>
<td>0.51</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>4.3</td>
<td>4.2</td>
<td>2.4–4.8</td>
<td>0.24</td>
</tr>
<tr>
<td>Percentage of cortex affected (%)</td>
<td>20</td>
<td>17</td>
<td>0–90</td>
<td>0.61</td>
</tr>
<tr>
<td>Width of the lesion (mm)</td>
<td>66.5</td>
<td>71.1</td>
<td>46.2–96.2</td>
<td>0.09</td>
</tr>
<tr>
<td>Length of the cortex (mm)</td>
<td>37.6</td>
<td>43.5</td>
<td>3.8–150</td>
<td>0.21</td>
</tr>
<tr>
<td>Survival time (d)</td>
<td>125.5</td>
<td>107</td>
<td>28–370</td>
<td>—</td>
</tr>
<tr>
<td>Compression surface affected (No. of dogs)</td>
<td>19</td>
<td>11</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bone biopsy performed (No. of dogs)</td>
<td>6</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tumor type</td>
<td>50</td>
<td>28</td>
<td>—</td>
<td>0.09</td>
</tr>
<tr>
<td>Osteosarcoma versus all other tumor types (No. of dogs)</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Univariate analysis identified potential variables considered in a multivariable logistic regression model evaluating the association of factors identifiable at radiographic diagnosis with the eventual development of pathological fracture present at necropsy. Variables identified (P < 0.20) were then evaluated in a multivariable model.

—— = Not applicable. CBPI = Canine Brief Pain Inventory. 20

On multivariable logistic regression analysis, age, bone affected, and lytic appearance at diagnosis were significantly (P < 0.05) associated with the eventual development of pathological fracture. Controlling for bone affected and lytic appearance, for every 4-year increase in age at diagnosis, the odds of fracture increased by 2.42 (95% confidence interval, 1.07 to 5.49; P = 0.034). Tumors of the radius were significantly (P = 0.03) less likely to develop pathological fracture, compared with other bones. Controlling for age and lytic appearance, tumors in bones other than the radius had odds of eventual fracture 5.05 as great as the odds in tumors of the radius (95% confidence interval, 1.46 to 17.4; P = 0.010). Controlling for age and bone affected, tumors that appeared lytic on radiographs at diagnosis had odds of eventual fracture 3.22 as great as the odds in tumors that appeared blastic or mixed lytic or blastic (95% confidence interval, 1.15 to 9.09; P < 0.026). On the basis of our model, none of the variables evaluated including histopathologic features, radiographic measurements, serum biochemical analyses, or physical examination findings were significantly associated with the development of pathological fracture.

Discussion

In the present retrospective study of 84 dogs with appendicular primary bone tumors managed medically at a pain clinic over a 6-year period (2007 to 2013) and evaluated by means of radiography with the diagnosis confirmed on eventual necropsy, results suggested that radial primary bone tumors were less likely and lytic tumors more likely to fracture. Pathological fracture is relatively rare in human patients with appendicular osteosarcoma, with only 5% to 10% of cases presenting as a pathological fracture or progressing to develop a fracture during treatment.10,11 The incidence of appendicular osteosarcoma and pathological fracture in dogs was believed to be similar, but there is a lack of evidence.10,11 The incidence of pathological fractures in the present study was considerably higher than we had anticipated on the basis of current literature. Because the gold standard for management of aggressive bone neoplasms has been surgical amputation, rather than medical management, this may have falsely lowered the reported incidence in dogs. In addition, dogs that undergo pain management alone in general practice are not generally systematically followed through to death. Often, because these are terminal cases, analgesics and anti-inflammatories are liberally prescribed for the remaining life of the dog and there is not documentation of bone integrity at the time of death or euthanasia. As such, the true frequency of this outcome is not well documented. In addition, dogs aggressively managed in...
a pain clinic may not be representative of the general population. The dogs in the present report were enrolled in one of several different pain management clinical trials and were therefore aggressively treated with a variety of analgesics and systematically followed from study enrollment until death. Multimodal therapy was used, and dogs were typically treated with 2 or more of the following: opioids, tramadol, NSAIDs, gabapentin, neurotoxins, and amantadine. There is the possibility that increased comfort afforded by management in a pain clinic may allow dogs to use their leg more, making a pathological fracture more likely. Whereas stress or mechanical weakness caused by diagnostic biopsy and necrosis of the tumor after radiation therapy may contribute to the development of fractures, this was not clinically apparent in the current study; however, the number of patients evaluated by means of biopsy was relatively small (n = 6). Future studies evaluating radiation therapy alone or in combination with bone biopsy should be performed to determine whether these are prognostically relevant for pathological fractures.

Previous studies indicated that osteosarcoma developed more frequently in the thoracic limbs of dogs versus the pelvic limbs, which may be related to the fact that the thoracic limbs support approximately 60% of the body weight in dogs. The present study agreed with previous accounts, with 52 of 85 (61%) affected limbs being thoracic. Radiographic measurements, including percentage of cortex affected, percentage of bone width affected, whether adjacent bone or joint was affected, maximal axial cortical involvement, length of the most severely affected cortex, and whether the compression surface of the bone was affected, had no significant association with pathological fracture formation in this study. Only the bone affected, lytic appearance, and age were significantly associated with pathological fracture.

Tumors of the radius were less likely to develop a pathological fracture, compared with other bones in the present study. This is consistent with the commonly held belief that the radius with its internal splint of the ulna is more resistant to fracture forces than solitary bones. Interestingly, the fibula does not seem to account for the same stability as the ulna. Within the thoracic limb, the radius and ulna transmit equally the forces applied through them at the level of the elbow, whereas minimal force is shared between the tibia and fibula at any level. Additionally, the ulna directly articulates with the humerus, while the fibula only has a synostosis with the tibia and no articulation with the femur. Studies have also illustrated that maintenance of the interaction of the radius and ulna with the interosseous ligament is critical in maintaining equal force transmission through the elbow joint. Disruption of the ulna distal to this ligament does not change the forces acting through the elbow joint as the majority of the forces distal to the interosseous ligament travel through the radius. As such, this may explain why tumors of the proximal aspect of the radius may be protected against fracture but does not explain why distal radial tumors do not appear to fracture.

The humerus had lower odds of fracture, compared with pelvic limbs in this study, although this difference was not significant (P = 0.18). Force plate evaluation of healthy dogs has indicated that whereas the peak vertical force is greater in the thoracic limbs than the pelvic limbs, the thoracic limbs actually have a higher braking impulse than the pelvic limbs. Conversely, the pelvic limbs have significantly higher propulsive impulse than the thoracic limbs. As such, whereas the peak force on the thoracic limbs may be greater, it appears that this has a slightly more gradual transition to peak force, compared with the pelvic limbs. This may be due to the elastic capacity of the muscles of the thoracic limb as well as the extrinsic musculature that transfers the force to the rest of the body. This elastic capacity may act as a shock absorber and help protect against high-impact energy and subsequent fracture of tumors of the thoracic limb.

Osteosarcoma was the most common primary bone neoplasm evaluated in the present study, representing 92% (78/85) of the neoplasms identified. This is consistent with previous studies. We did not identify any significant difference in the fracture rate for the other tumor types found, but this may be secondary to the very low number of cases for the other types of neoplasms in this series. A single dog was identified with squamous cell carcinoma on the basis of results of histopathologic examination. This is an extremely rare primary bone neoplasm because of the lack of native epithelial cells in appendicular bone tissue and may indicate a metastatic lesion. There are 3 reports of appendicular primary squamous cell carcinoma in human patients. A full necropsy could not identify a primary squamous cell carcinoma location and as such this dog was included in the current study. Additionally, whereas the dog with 2 tumors might seem like an outlier, both tumors (one located at the radius and the other at the tibia) were located at the metaphyseal region, which is more consistent with primary neoplasia rather than a metastatic lesion. The proximal tibial lesion was also a site of a previous TPLO surgery, and histopathologic examination indicated moderate amounts of cartilage differentiation, whereas the site at the distal aspect of the radius showed minimal cartilage differentiation. As such, this dog was considered to have 2 primary tumors.

An elevation in serum alkaline phosphatase activity has previously been associated with a poorer prognosis in dogs with osteosarcoma. The present study found no significant association between alkaline phosphatase activity or any other biochemical parameter evaluated and likelihood of fracture. The median survival time of patients in this study was 111 days (range, 28 to 447 days). This is consistent with previous studies that have evaluated amputation alone as treatment for osteosarcoma. Because the median survival time with pain management alone did not vary significantly from historical studies evaluating amputation alone, it could be considered as a viable alternative for patients that have contraindications to amputation or when owners cannot afford radiation therapy as long as signs of pain can be controlled medically. Because the median survival time in this study was similar to that reported by others for patients treated by means of amputation, we suggest that pain management may be considered a viable alternative; however, this will require further investigation.
Whereas histologic subtype has been reported to have no prognostic importance, little research has evaluated tumor subtype or grade and its associated fracture rate.\(^1\)\(^,\)\(^2\) Osteosarcoma usually originates from elements within the medullary canal (intramedullary or endosteal osteosarcoma). Few tumors are considered juxtacortical or originating from the periosteum. These tumors are usually primarily osteoblastic with very mild amounts of cortical lysis. The present study identified 9 cases where the primary radiographic appearance was blastic. These cases may represent the slower-growing periosteal osteosarcoma, although this was not evaluated histologically. The lytic nature of the bone tumor being associated with ultimate pathological fracture was not surprising. Several studies in human patients report a higher risk of fracture for lytic lesions.\(^3\)\(^,\)\(^4\) In the present study, the majority of lesions (49%; \(n = 42\)) were assessed as mixed. The rate at which mixed lesions fractured was less (15/42 [37%]) than the rate for lytic lesions (17/34 [50%]). Lytic lesions may represent a more advanced process in local bone resorption. Major limitations of the present study include the retrospective nature of the study. Whereas patients were prospectively followed through the pain clinic, the exact date of onset of fracture could not be determined. Initial radiographs taken were of mixed quality and did not always include orthogonal views. Patients also received many different pain management drugs and protocols.

Results of this study illustrated that tumor location and the lytic appearance of the bone at diagnosis were significantly associated with the development of pathological fractures in dogs. The incidence of pathological fracture secondary to primary appendicular neoplasia may be higher than previously suggested, and further investigation of aggressive pain management on the development of pathological fractures is suggested. This may better inform clinicians counseling owners who are considering amputation and other treatment options.

References

Evaluation of serum amyloid A and haptoglobin concentrations as prognostic indicators for horses with inflammatory disease examined at a tertiary care hospital

Trina L. Westerman et al

**Objective**—To evaluate use of serum amyloid A (SAA) and haptoglobin concentrations as prognostic indicators for horses with inflammatory disease in regard to euthanasia, complications, and hospitalization duration and cost.

**Animals**—20 clinically normal horses and 53 horses with inflammatory disease.

**Procedures**—Total WBC count, neutrophil count, and fibrinogen, SAA, and haptoglobin concentrations were determined for clinically normal horses and horses with suspected inflammatory disease. Clinicopathologic values at admission were compared to test the use of SAA and haptoglobin concentrations in predicting euthanasia, complications, and hospitalization duration and cost. Haptoglobin and SAA concentrations of 22 horses were monitored during hospitalization to test the use of serial measurements in predicting survival and complications.

**Results**—Neutrophil count and SAA and haptoglobin concentrations were significantly different at admission for horses with inflammatory disease, compared with those for clinically normal horses. Horses with colitis and peritonitis had significantly higher SAA and haptoglobin concentrations than clinically normal horses. A moderate positive correlation (r = 0.355) between hospitalization duration and haptoglobin concentration was identified. Horses with an increase in SAA concentration between 24 and 72 hours after admission, compared with admission SAA concentration, were significantly more likely (OR, 7.0; 95% confidence interval, 1.1 to 45.9) to be euthanized or develop complications.

**Conclusions and Clinical Relevance**—Concentrations of SAA and haptoglobin at admission were not significantly correlated with outcome in horses with inflammatory conditions. Acute-phase proteins likely have more utility in serial analysis rather than testing at a single time point for horses with inflammatory conditions. (Am J Vet Res 2015;76:882–888)