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Case Study

Osteosarcoma in Baboons (*Papio* spp)

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Bone neoplasms in baboons (*Papio* spp) are rare, with only one confirmed case of osteosarcoma previously described in the literature. Over a 12-y period, 6 baboons at a national primate research center presented with naturally occurring osteosarcoma; 3 lesions affected the appendicular skeleton, and the remaining 3 were in the head (skull and mandible). The 6 cases presented were identified in members of a large outdoor-housed breeding colony. The subjects were not genetically related or exposed to the same research conditions. Diagnoses were made based on the presentation and radiographic findings, with histologic confirmation.

Neoplasia remains a highly prevalent condition across the majority of species. A recent survey of a large baboon colony identified 395 neoplasms among 4297 animals.[6] The most common neoplasms documented in NHP include lymphosarcoma, adenocarcinoma, and squamous cell carcinoma.[8] Tumors involving the musculoskeletal system are much rarer than are the other previously mentioned types. The musculoskeletal neoplasms reported most prominently in the literature are osteoma, osteosarcoma, odontoma, and various types of myxoma, with *Macaca* spp being the NHP affected most often.[5] However, this apparent prevalence may be artifactual due to the use of far more animals of *Macaca* spp compared with other NHP species.

Osteosarcoma is an infrequently documented neoplasm among NHP, and it is particularly rare in baboons (*Papio* spp.). Combined-type osteosarcoma in a rhesus macaque,[4] extraosseous osteosarcoma in a rhesus macaque,[17] and osteoblastic osteosarcoma in a gray mouse lemur have been reported.[18] Among 4 reported cases of bone tumors in baboons, only one was confirmed as osteosarcoma and involved the mandibular ramus of a male baboon.[8,12,24] Another neoplasm, identified on the distal aspect of the right ulna of a baboon, initially was described in a review article as a giant cell tumor[22] but was later referred to as a fibrosarcoma[23] and then as an osteosarcoma,[19] thus making the confirmed diagnosis unclear. The remaining 2 known cases of bone tumors in baboons were osteomas present in the tibia and femur.[8,12] Three other osteosarcomas were included in reviews of pathology from the Southwest National Primate Research Center (San Antonio, TX), but detailed clinical and pathologic information was not described.[6,7,9]

Case Reports

Over the previous 12 y, 6 baboons (*Papio* spp) with a confirmed diagnosis of osteosarcoma have been identified at the Southwest National Primate Research Center. The approximate average population of baboons at this facility during this time was 3300 animals, with an average life span of approximately 20 y. All animals were housed under an IACUC-approved housing protocol in accordance with the *Guide for the Care and Use of Laboratory Animals*,[13] Public Health Service Policy,[20] and Animal Welfare Act[2] and Regulations[3] at an AAALAC-accredited institution. The baboons received a commercial diet (15% crude protein, 4% crude fat, 5% crude fiber; Purina 5 LEO Monkey Diet, Purina Mills, St. Louis, MO) once daily and municipal tap water ad libitum. Fresh produce or grains were offered daily as edible enrichment items. Baboons were housed in outdoor group-housing pens in which shelter from the elements was available. The entire colony was exposed to the same weather and housing conditions. All baboons were provided with manipulable enrichment (including balls, Kongs, and toys) as well as continuous social interaction with conspecifics. All animals were tuberculosis free as determined by semiannual skin testing. Necropsy and histologic evaluation were performed by board-certified veterinary pathologists. Microscopic findings that were equivocal or otherwise challenging were reviewed by 3 to 5 other board-certified veterinary pathologists. As deemed necessary, cases were referred to the Joint Pathology Center, the Armed Forces Institute of Pathology, or to additional other pathologists with expertise in the field. In the following case series we discuss each of the 6 cases that presented to the clinic for evaluation and the methods and assays used to reach the diagnosis of osteosarcoma.

Case Studies

Case 1 involved a 13-y-old female *Papio hamadryas anubis* that developed a large, firm mass that was inoperable in the inguinal region. The mass was deep in the tissue, very vascular, and contained bone fragments. Results of CBC and chemistry analyses showed no significant findings, and thoracic radiographs were normal. The animal was euthanized and submitted for necropsy. At necropsy, the mass measured 6 cm × 6c m and was attached to the pelvis adjacent to the coxofemoral joint. No other gross lesions were noted on examination. Histopathology revealed a variably cellular, poorly demarcated, unencapsulated, infiltrative mass composed of abundant irregularly arranged osteoid and bone that replaced preexisting soft tissues. The cells were spindloid to stellate with indistinct cell borders, eosinophilic cytoplasm, large

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oval to round nuclei, a high nuclear:cytoplasmic ratio, and 1 or 2 prominent magenta nucleoli. Moderate anisokaryosis, pleomorphism, and occasional multinucleated cells were present; mitoses were not noted.

The baboon in case 2 was a 7-y-old female *Papio hamadryas anubis* × *Papio hamadryas cynocephalus* crossbreed that had a bony growth that protruded from the back of the skull (Figure 1 A). CBC and chemistry analyses yielded no significant findings. The animal was treated with antibiotics and tramadol. An abscess developed superficial to the bony prominence, and eventually a gaseous, foul-smelling substance was expressed when the infection persisted despite treatment. The animal was euthanized and submitted for necropsy. Necropsy revealed a massive, proliferative, firm mass that extended from the dorsum of the skull, primarily on the right side (Figure 2 A). The central area of the lesion was soft and caseous. An area of proliferation had caused subjacent thickening of the calvarium, but the main body of mass was exterior to the calvarium. The lungs contained firm, raised masses consistent with metastatic neoplasia (Figure 2 B). Histopathology revealed a highly cellular, moderately well demarcated, unencapsulated, somewhat lobulated mass composed of abundant irregularly arranged osteoid and rare bone with some mineralization, extending primarily outwardly from the surface of the calvarium. The cells had indistinct cell borders, with pale eosinophilic cytoplasm, round to oval nuclei, a high nuclear: cytoplasmic ratio, typically one prominent nucleolus, and as many as 5 mitoses per 400× field (Figure 2 E). There was moderate anisokaryosis and pleomorphism. The pulmonary lesions were similar to those in the skull.

In case 3, an 8-y-old female *Papio hamadryas anubis* presented with a large mass on the left distal femur with a proliferative (Figure 1 B), osteolytic appearance and a history of chronic weight loss. CBC and chemistry analyses yielded no significant findings, and thoracic radiographs were normal. The animal was euthanized and submitted for necropsy. During necropsy, a large (10 cm × 6 cm × 2 cm) bony mass was noted in the distal femur. No other gross lesions were present. Histopathology revealed a moderately cellular, poorly demarcated, unencapsulated, infiltrative mass composed of abundant irregularly arranged osteoid, bone, and occasional fibrous tissue that expanded the marrow and replaced preexisting bony trabeculae. The cells were generally spindle-form but polygonal in lacunae, with indistinct cell borders, abundant pale eosinophilic cytoplasm, and large oval nuclei with prominent, usually single, magenta nucleoli and loosely arranged chromatin. There was moderate anisokaryosis and pleomorphism; mitoses were not noted. Extensive areas of coagulative necrosis were present within the mass.

The baboon representing case 4 was a 9-y-old female *Papio hamadryas anubis* × *Papio hamadryas cynocephalus* crossbreed that had a large palatine mass involving the soft and hard palates and a large swelling on the upper left muzzle. CBC and chemistry analyses showed no significant findings, only a slight elevation in ALP (606 U/L; range, 0 to 560 U/L). Treatments consisted of antibiotics and NSAID. The animal was euthanized and submitted for necropsy. Necropsy demonstrated a sessile, lobulated hard mass that replaced the soft palate and extended into the oral cavity, filling more than 90% of the overlying sinuses (Figure 2 C). The left side of the nasal bone was elevated and displaced. Histopathology revealed a moderately cellular, poorly demarcated, mass that expanded and replaced preexistent bony tissue and extended variably into the surrounding soft tissues. The mass was composed of abundant irregularly arranged osteoid, fibrous tissue, and woven bone trabeculae. The cells had indistinct cell borders; were spindle-form to polygonal in fibrotic and bony areas, respectively; contained moderate amounts of amphophilic to basophilic cytoplasm; and had oval to polygonal nuclei with light to moderately stippled chromatin and a single prominent nucleolus (Figure 2 F). Mitoses were not noted. Multinucleate cells were frequently observed associated to bony trabeculae.

In case 5, a 7-y-old male *Papio hamadryas anubis* presented with bone exposure on the lower left mandible and bone chips surrounding the canine (Figure 1 C). The mass grew to encompass the entire chin area. CBC and chemistry analyses showed no significant findings, and thoracic radiographs were normal. NSAID were used as pain management. The animal was euthanized and submitted for necropsy. During necropsy, a 7-cm bony mass of the mandible, primarily involving the left side, was noted (Figure 2 D). Histopathology revealed an expansile, relatively well demarcated, mass composed of abundant irregularly arranged osteoid and woven bone trabeculae surrounded by loose connective tissue containing abundant adipocytes and large vascular spaces. Large, spindloid to irregularly shaped cells lined the trabeculae and were within both lacunae and the loose connective tissue. The cells had abundant pale eosinophilic cytoplasm and large oval nuclei with prominent, usually single, magenta nucleoli and loosely arranged chromatin. There was moderate anisokaryosis and pleomorphism. Mitoses were infrequent. Osteoclasts were fairly common. The epithelium covering the mass was ulcerated and contained many inflammatory cells.

Case 6 involved a 15-y-old female *Papio hamadryas anubis* × *Papio hamadryas cynocephalus* crossbreed that originally presented for acute nonweight-bearing lameness of the right leg. Radiographs revealed an aggressive osteolytic lesion of the distal diaphyseal and metaphyseal region of the right femur but did not demonstrate any changes to the stifle joint (Figure 1d). CBC and chemistry analyses showed no significant findings. The animal was treated with antibiotics and pain medications but did not improve clinically. A bone biopsy revealed probable osteosarcoma. Thoracic radiographs showed areas consistent with metastases throughout all fields. The animal was euthanized and submitted for necropsy. During necropsy, the distal aspect of the femur was noted to be nonmineralized and mainly consisted of firm tissue. Histopathology revealed a hypocellular, generally well demarcated, expansile and sometimes infiltrative mass composed of dense, mature fibrous tissue with small spindloid cells that replaced and entrapped preexisting muscle and bone. Throughout the mass were islands of loosely arranged fibrous tissue with large pleomorphic cells. There were also scattered areas of large, pleomorphic, spindloid to stellate cells with basophilic cytoplasm, large oval to round nuclei with a high nuclear:cytoplasmic ratio, 1 to 3 nucleoli, and 1 to 3 mitoses per 400× field; these and multinucleated cells lined areas of osteoid, mineralized matrix, and bone spicules. A lung nodule contained large spindle-form cells with eosinophilic cytoplasm, large nuclei, a high nuclear:cytoplasmic ratio, 1 to 3 nucleoli, 1 to 3 mitoses per 400× field, and moderate amounts of fibrous tissue stroma.

Discussion

According to the current literature, osteosarcoma is extremely rare in baboons (*Papio* spp). To our knowledge, this report is only

Figure 1. Radiographic images from cases of baboon osteosarcoma. (A) Case 2. Expansile lesion on skull. (B) Case 3. Osteoproliferative growth on left femur. (C) Case 5. Osteoproliferative growth of mandible. (D) Case 6. Osteolytic region of right leg.

the second description of confirmed osteosarcoma cases in baboons (*Papio* spp). There are few reports of osteosarcoma and osteoma in pathology surveys of baboons.[6,7,9] Primary bone tumors typically occur in the metaphysis and usually do not cross joints until the disease has progressed and the lesion has enlarged.[28] The tumors can metastasize to parenchymal organs and other bones. By the time a diagnosis is made, metastasis has often already occurred.[28] The current case study features a very rare disease in baboons, and each of the cases included had a unique clinical presentation that required multiple diagnostic evaluations to determine a diagnosis. Because of the rarity of bone tumors in baboons (*Papio* spp), especially osteosarcoma, clinicians need to consider a wide range of differential diagnoses when choosing diagnostic tests and treatments.

Osteosarcomas originate from mesenchymal stem cells and produce osteoid.[10] This neoplasm is prone to metastasize to other locations, and metastasis typically is the cause of death when the disease is allowed to progress.[10] Although radiographs obtained at the time of diagnosis often fail to reveal metastatic disease, it frequently develops after the primary tumor is controlled, leading to the notion that metastasis occurs early in osteosarcoma.[10] Osteosarcoma is the most common tumor of the long bones of humans, dogs, and cats,[10,21,28] in which the most common lesion sites are the proximal humerus, distal radius, distal femur, and proximal tibia. Because this neoplasm usually originates in the metaphyses of long bones, the typical presentation associated with osteosarcoma is lameness in the affected limb. In addition, the animal may exhibit muscle atrophy of the affected limb, lethargy, and anorexia. It is yet to be determined whether this distribution is consistent in baboons, given the paucity of documented cases, but in 3 of the 6 cases we present here, the neoplasm involved the skull, and metastasis to the lung occurred in 2 of the 6 cases. Osteosarcoma shows a bimodal age distribution in humans and dogs[10,28] but not cats.[28] In comparison, the cases we described here all occurred in middle-aged baboons, with a predominance in female baboons (5:1). However, this apparent sex-associated predilection may merely reflect the female:male ratio in the colony during this time period. Specifically,the baboon population was

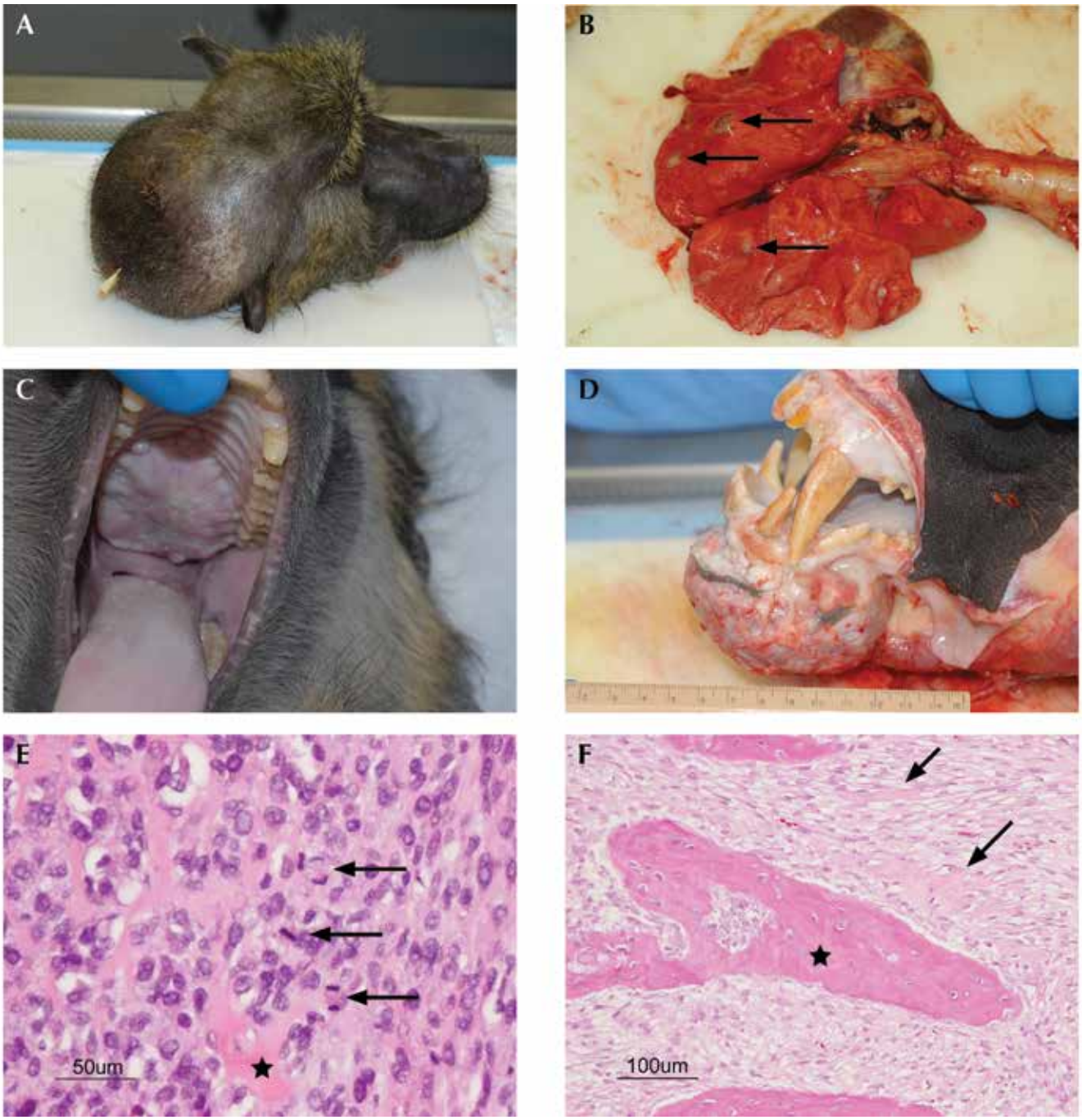

Figure 2. Pathology findings from cases of baboon osteosarcoma. (A) Case 2. Expansile lesion on skull. (B) Case 2. Metastatic foci in lungs (arrows). (C) Case 4. Irregular, sessile palantine mass. (D) Case 5. Osteoproliferative growth of mandible. (E) Case 2. Area of anaplastic sheets of cells with osteoid formation (*) and mitotic figures (arrows). (F) Case 4. Palantine osteosarcoma. Moderately cellular interlacing bundles of neoplastic cells with osteoid formation (arrows) and islands of woven bone (*).

63% female and 37% male, with average ages of 8.3 y (female) and 5.6 y (males) and a maximal life span of 30 y.

Typically, osteosarcoma is diagnosed on the basis of radiographic findings and confirmed by using histopathology. Radiographically, osteosarcoma can appear lytic, sclerotic, or (most commonly) mixed lytic and sclerotic.[28] Bone biopsies can be obtained but may not be diagnostic, and care should be exercised to prevent fracturing the limb. Osteosarcomas vary widely in histologic appearance.[27] Osteosarcoma neoplastic cells are typically spindloid but can vary in size and shape. These cells produce extracellular matrix that may be predominantly osseous, cartilaginous, or fibrous and leading to the subtype classification of lesions as osteoblastic, chondroblastic, or fibroblastic, respectively.[15] The histologic feature necessary for a diagnosis of osteosarcoma is the presence of osteoid or bone production by neoplastic cells. Multiple systems have been established for grading osteosarcoma

and are based on cell type and location and grade of tumors, but the marked variations between osteosarcomas as well as within a single lesion render tumor grading of osteosarcomas an unrewarding exercise.[27] One treatment option is amputation of the affected limb, but osteosarcomas can recur in a different site, and amputation often does not prolong life, as indicated by the typically poor prognosis associated with this type of neoplasia.[10] Although amputation was considered for the cases that involved the long bones of baboons, the overall health and utility of the baboons within the breeding colony and their suitability for use in research projects made this option impractical for the cases presented.

Differential diagnoses for the sclerotic, lytic, or mixed bone conditions in our baboons included osteomyelitis, osteoid osteoma, osteoblastoma, osteochondroma, ossifying fibroma, fibrous dysplasia, and myelofibrosis. The most common differential diagnoses considered among all cases were osteomyelitis and cancer of any type; either of these diagnoses leads to euthanasia for final determination. Osteoid osteoma and osteoblastoma are similar in that they both have a central pattern of growth, with calcified trabeculae and woven bone lined with osteoblasts, some osteoclasts, and a vascular fibrous stroma, but the distinct difference is that osteoid osteoma is typically intracortical, and osteoblastoma is intramedullary.[16] On histology, osteoblastoma has permeative growth of the intratrabecular space and lacks maturation toward the edges of the lesion, thus distinguishing osteoblastoma from osteosarcoma.[11] Unlike osteoblastoma and osteosarcoma, osteochondroma lacks permeation of trabecular bone and is the most common precursor lesion for secondary chondrosarcoma.[11] Fibrous dysplasia is typically a benign disorder in which normal bone is replaced by fibrous tissue; this abnormality is more common in young compared with mature patients.[26] Although the lesions are similar, ossifying fibroma is characterized by the presence of active osteoblasts cover the trabeculae thus making it histologically distinct from fibrous dysplasia.[1,25] Myelofibrosis is a myeloproliferative disorder that develops secondary to fibrosis of the marrow.[14] It is important to consider all of these conditions when diagnosing cases involving the musculoskeletal system. We recommend the use of histopathology to confirm a diagnosis in preparation for treatment.

The animals represented in these 6 cases are among the rare population of baboons that have been diagnosed with osteosarcoma. Evaluation of their medical records failed to indicate any similarities in lineage or research project involvement that might have contributed to an increased predisposition of osteosarcoma development. Specifically all of the baboons with tumors were included only in studies that involved blood sampling or modified diets that differed in their fat contents; neither of these features is likely to predispose the animals to developing osteosarcoma. Apparently all of these lesions were spontaneous findings and idiopathic in nature. Additional research may be warranted to determine whether any inherent factors predisposed this select group of animals to the development of osteosarcoma.

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