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Department of Veterinary Pathology
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Conference Moderator: Dr. Steven Weisbrode, Diplomate ACVP
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Dept of Veterinary Biosciences
Columbus, OH

CASE I – VET UFMG 26974 (AFIP 2988265)

Signalment: Adult, male paca *Agouti paca*.

History: This is one of five pacas (*Agouti paca*) that developed lameness (Fig. 1). They were kept in captivity within an environmental reservation, and they were fed fruits and vegetables with a small amount of corn and a commercial rabbit food, according to FAO's recommendations (1995). They received water free of fluoride or any other chemical or microbiological contaminant. The animal was submitted for euthanasia due to poor prognosis.

Gross Pathology: Cranial bones were markedly thickened (Figs. 2-4). Long bones had a very thick cortex and replacement of trabecular bone by compact bone, resulting in reduction of the marrow cavity. The vertebrae had exostoses that projected into the vertebral canal (Fig. 5), compressing the spinal cord. Radiologically, in addition to these gross lesions there was an increased radiodensity of the whole skeleton (Fig. 6).

Histopathologic Description: Marked increase in the amount of compact bone tissue, characterized by narrowing of the Haversian canals and large number of cement lines giving a mosaic appearance to the tissue (Fig. 7). In all long bones, the trabeculae were thickened and coalescing, with substitution of trabecular bone by osteonic bone, and retention of cartilage (chondroid core) in the metaphysis. There were several pyknotic osteocytes within enlarged lacunae, and a large number of empty osteocytic lacunae (Fig. 8) with multifocal disintegration of the bone matrix, characterizing osteonecrosis (not seen in all sections submitted).

Contributor's Morphologic Diagnosis: Bone. Osteopetrosis, generalized, severe. Osteonecrosis, multifocal, moderate. *Agouti paca*.

Contributor's Comment: Osteopetrosis is a metabolic disease of bone, characterized by osteomegaly or increased amount of bone tissue per unit of volume. The most common cause of osteopetrosis is nutritional hypercalcitoninism that induces a reduction in bone resorption and consequently an increase in the amount of bone.

Osteopetrosis has been diagnosed in cattle both as a congenital condition^{1,2} or as a metabolic condition secondary to nutritional imbalance³. Osteopetrosis has also been described in other species including mice, rats, rabbits, man and the manatee, in which it is physiologic (reviewed by 1). In man, osteopetrosis is a rare genetic disease also known as Albers-Schonberg disease and marble bone disease⁴, which is due to an imbalance in bone remodeling due to a defect in bone resorption due to impaired osteoclastic activity (reviewed by 4). In mice, osteopetrosis is associated with lack of colony-stimulating factor 1 activity (*op/op* mice), which is associated with defective macrophage and osteoclast differentiation⁵. To our knowledge these are the first cases of osteopetrosis diagnosed in paca (*Agouti paca*).

AFIP Diagnosis: Long bone, epiphysis and metaphysis: Osteosclerosis, diffuse, severe, paca (*Agouti paca*), rodent.

Conference Comment: Attendees received a section of long bone with epiphysis and metaphysis; others will have received a similar slide or a slide with a section suspected of being intervertebral disc and adjacent bone or facets.

Conference attendees briefly discussed osteopetrosis as a clinical term used to describe osteosclerotic changes in bone. Osteopetrosis is an acquired or congenital disease of excess bone due to a failure of resorption; not increased formation. Osteosclerosis is an increase in bone mass resulting from the failure of osteoclasts to resorb and model primary trabeculae or, more simply, increased density of normal appearing bone. Osteosclerosis affects bones that elongate by endochondral ossification from a growth plate. Grossly, affected bones are dense and have no medullary cavity. Microscopically, retained primary trabeculae form spicules of bone with central cores of calcified cartilage which fill the medullary cavity (6). The contributor listed several species in which osteopetrosis occurs. In addition, avian leukosis virus causes osteopetrosis in poultry (7).

In this case, osteosclerosis occurs in both the epiphysis and metaphysis. There is retention of longitudinal cartilage septa with retained cartilage cores and the

presence of osteons with minimal porosity in the medullary bone indicating a defect in remodeling. As described by the contributor, there is marked mosaic patterning in the compacted regions of the epiphysis and metaphysis. Additional features include fibrous tissue on the articular surface, thin, irregular articular cartilage and the presence of very little marrow. In some sections there is also periosteal new bone formation indicating a defect in modeling as well.

The terms modeling and remodeling can be confusing. Modeling describes the change in shape or contour of a bone in response to normal growth, altered mechanical use, or disease. Modeling allows the shape or size of bone to change and enables the medullary cavity to enlarge and the overall shape of the bone to be maintained while the bone is growing. Remodeling is the constant replacement of old bone with new bone which allows for the repair of accumulated microscopic injury (microfractures). It is interesting to note that in mice, rats and several other small species, cortical bone is not remodeled (6).

The cause of osteosclerosis in this case is not apparent. The paca is described as an adult; however, sexual maturity and skeletal maturity do not necessarily coincide. Assuming the paca is skeletally mature, and this lesion does not represent a heritable trait, consideration was given to hypervitaminosis D. Chronic hypervitaminosis D (e.g. prolonged ingestion of vitamin D containing plants) results in hypercalcemia which causes chronic lowering of parathormone (PTH) and elevation of calcitonin, effectively stopping bone resorption (6).

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<http://www.vet.ufmg.br>

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CASE II – CSU 05-06 Case#1 (AFIP 2985156)

Signalment: A newborn Peruvian Paso breed equine.

History: A history of an uneventful parturition, progressive weakness and eventual collapse.

Gross Pathology: Generalized sclerosis of axial and appendicular skeleton (Fig 1), multiple rib fractures, and brachygnathia inferior.

Radiographic Results: Regionally extensive increases in radiodensity (sclerosis) affecting all bones. In the vertebral column, this creates a "butterfly-like" effect (Fig. 2).

Histopathologic Description: The submitted slides consist of longitudinal sections through one of either the fifth, sixth, or seventh thoracic vertebrae. In each of the sections, the medullary spaces of the primary and secondary ossification centers are nearly obliterated by a disorganized meshwork composed of interweaving trabeculae of retained primary spongiosa. Each of the trabeculae consists of a central core of cartilage that is segmentally capped by superficial plates of osteoid or bone. Within the center of the primary ossification center, there are radiating trabeculae of predominantly woven bone with small amounts of lamellar bone and occasional islands of cartilage. There is segmental and irregular thickening of the growth plates, which occasionally project uneven tongues of cartilage into both the primary and secondary ossification centers. Increased numbers of osteoclasts are present, both within, and outside of, Howship's lacunae. Osteoclasts are often characterized by increased nuclear number, nuclear disorganization, and intracytoplasmic vacuolization (Fig 3), as compared to an age-matched control (Fig. 4). There is a reduction in marrow tissue in which the remnant medullary spaces contain decreased numbers of hematopoietic cells admixed with occasional bands of fibroblastic connective tissue, numerous lakes of hemorrhage, and strands of fibrin.

Contributor's Morphologic Diagnoses: Vertebrae: Medullary hyperostosis, chronic, regionally extensive, severe with retention of spongiosa and failure of bone resorption.

Contributor's Disease Diagnosis: Equine osteopetrosis

Contributor's Comment: Osteopetrosis is a clinically and genetically heterogeneous group of relatively rare skeletal disorders characterized by regional to generalized osteosclerosis, or increased skeletal mass. They are generally considered to be inherited diseases and have been reported in both humans and in many domestic species, including the calf, foal, cat, dog, mouse, rabbit, and sheep.⁴ In those species in which it has been determined (human and calf), the pattern of inheritance is typically autosomal recessive. In osteopetrosis, the increase in bone mass is the result of an imbalance between the two arms of osteogenesis. That is, there is either increased bone production from osteoblasts or diminished bone resorption by osteoclasts. In mammalian species in which the pathogenesis is known, osteopetrosis typically occurs by the latter mechanism.

Due to osteoclast dysfunction, there is diminished bone modeling and remodeling, failure to resorb the primary spongiosa and the periosteal sleeve, and resultant accumulation of primary and/or secondary spongiosa. Additional clinical characteristics of the diseases include hematopoietic dysfunction, due to obliteration of medullary tissue, and cranial nerve dysfunction, including blindness and deafness, due to defective nerve foramina development.³

In osteopetrosis, the diminished osteoclast activity may be the result of one of the following three mechanisms:¹

1. Decreased number of osteoclasts.
2. Lack of osteoclast function.
3. Lack of the appropriate microenvironment.

In the osteopetrosis of domestic animals, as normal-to-increased numbers of mature-appearing osteoclasts are recognized microscopically, it is assumed that the defect is in osteoclast function.^{4,5} Although in the majority of the species, the specific derangement has yet to be clarified.

In previous reports of foal osteopetrosis, four of the five animals were, like the animal in this report, of the Peruvian Paso breed, strongly implicating a genetic etiology.¹ The final foal was an Appaloosa. As in other domestic species, the specific cellular defect in these foals is also uncertain. Based upon quantitative histomorphometric data, as compared to an age-matched control, the foal in this case had 25-300% greater numbers of osteoclasts depending upon the region of the bone examined. This finding supports the hypothesis that the defect involves

some manner of osteoclast dysfunction and is similar to findings in the previous equine reports.

Among domestic animals, osteopetrosis is best characterized in the calf. The disease has been reported in numerous breeds, including the Angus, Hereford, and Simmental breeds, and is a genetic condition with an autosomal recessive pattern of inheritance.⁴

In the calf, cat, and chicken, osteopetrosis-like lesions are reported in association with infection with bovine pestivirus (BVD), Feline leukemia virus, and Avian leukosis virus, respectively. In humans, osteopetrosis has been classified according to its clinical phenotype (juvenile vs. adult forms and “malignant” vs. “intermediate” forms), its pattern of inheritance and its genotype. The most common genetic mutations in humans involve a dysfunctional membrane bound proton pump, which is responsible for acidifying the extracellular digestion chamber (w/in the Howship’s lacunae) or a dysfunctional Cl⁻ anion exchanger that no longer acts to maintain electroneutrality.^{3,5}

AFIP Diagnoses: Bone, thoracic vertebrae (per contributor): Osteosclerosis with failure of modeling of primary trabeculae, Peruvian Paso, equine.

Conference Comment: The contributor provides an excellent review of heritable equine osteopetrosis. Conference attendees debated the orientation of the section and the unexpected presence of additional growth plates in the developing neonatal vertebrae, which are interpreted as those of the vertebral arches. In this case, there is a total lack of modeling of the primary trabeculae in spite of high numbers of osteoclasts indicating an error in bone resorption.

In the Guides for Toxicologic Pathology, hyperostosis is defined as hypertrophy of bone, an abnormal increase in non-neoplastic skeletal bone mass which may be proliferative or non-proliferative (6). Attendees briefly discussed reserving the use of the term hyperostosis to denote increased bone mass due to increased dimension of bone; whereas, osteosclerosis more accurately denotes increased bone mass due to increased density of bone with normal dimensions.

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CASE III – H04-2593 (AFIP 2988634)

Signalment: 12-year-old, female (neutered), Staffordshire Bull Terrier, *Canis familiaris*, Canine

History: Sudden onset polyuria/polydipsia. The dog was euthanized 6 weeks after onset of clinical signs due to significant weight loss (despite a good appetite) and no response to symptomatic treatment.

Gross Pathology: The tissue submitted is from a 2.5 cm diameter hard nodule on the cranial mandible that displaces two incisors.

Additional findings on post mortem examination:

Lung – disseminated white foci (up to 5 mm in diameter) throughout both lungs (gross photo)

Mammary region – multilobular dark red/black mass (4 x 2 cm) with a blood-filled central cavity

Thyroid glands – disseminated white foci (up to 1 mm in diameter)

Liver – multifocal tan nodules (up to 1.5 cm in diameter) that are slightly raised from the surface with a depressed darker tan centre (umbilicated); see gross photo

Brain – multifocal dark brown/black areas (up to 5 mm in diameter) throughout the brain parenchyma (gross photo)

Pituitary gland – enlarged with a bulbous appearance and disseminated white foci (1 mm in diameter)

Pancreas – multinodular appearance with a firm texture. Multifocal dark red/brown areas (1-3 mm in diameter); see gross photos

Kidneys – focal hemorrhage (from biopsy); multifocal subcapsular depressions (chronic glomerulointerstitial nephritis)

Laboratory Results: Urine specific gravity: 1.005

Initial hematology revealed mild dehydration (slightly raised erythrocyte count, PCV and hemoglobin concentration)

Biochemistry revealed no significant abnormalities.

Low dose dexamethasone test revealed normal basal cortisol levels and levels < 28nmol/l at 3 and eight hours post dexamethasone administration (normal response).

Urinalysis revealed ++ protein

Renal Tru-Cut biopsy revealed moderate chronic glomerulointerstitial nephritis.

Histopathologic Description: Oral cavity/mandible, within which there is a subepithelial binodular mass composed of irregular islands of well-differentiated cartilage bordered by less differentiated chondroplastic tissue, which merge into poorly differentiated mesenchymal tissue. Multifocally, there are islands of irregular mature spongy bone and there is evidence of ossification of some of the cartilage. Occasional mitoses are seen in the poorly differentiated cells. Multifocally, within the cartilaginous and mesenchymal areas, and frequently within dilated vessels in the supporting stroma, there are lobules of neoplastic epithelial cells that occasionally form tubular structures; in the periphery of the lobules, the cells occasionally palisade. These neoplastic cells have poorly defined borders, moderate amounts of eosinophilic cytoplasm and round to oval nuclei with vesicular chromatin and multiple small nucleoli. Mitoses are variable in number, but in areas average 15-20 per high power field; occasional bizarre mitoses are seen. Apoptoses are common. There is moderate anisokaryosis. In most sections there is a mild superficial subepithelial plasma cell-dominated infiltration.

Contributor's Morphologic Diagnosis: Mandible: Multilobular tumor of bone with metastatic adenocarcinoma, Staffordshire Bull Terrier, Canine.

Contributor's Comment: Multilobular tumor of bone (formerly called multilobular osteochondrosarcoma, multilobular osteosarcoma, multilobular chondroma, multilobular osteoma, chondroma rodens, calcifying aponeurotic fibroma, cartilage analogue of fibromatosis and juvenile aponeurotic fibroma) is an uncommon tumor that is primarily observed arising from the flat bones of the skull of older, medium-sized to large dogs (occasionally seen in man, cats, horses and ferrets)^{1,2}. The gross appearance is of a hard nodular mass with discrete borders that generally ranges from 2 to more than 10 cm in diameter³. Histologically, the tumor is composed of numerous contiguous lobules of cartilage and/or bone bordered by septae of spindle cell mesenchyme². Multilobular tumors generally exhibit slow progressive growth and may cause clinical signs by compressing adjacent structures. Recurrence following excision is common and metastasis can occur. Multilobular tumors of bone have been graded using criteria including pushing/invasive borders, size of lobules, organization, mitotic index, cellular

pleomorphism and necrosis^{1,4}. Using these criteria, this mass was considered to be grade I.

In this animal, there was no history of clinical signs associated with the bone tumor. The extensive infiltration of the kidney by a metastatic simple mammary carcinoma, in addition to a pre-existing chronic interstitial nephritis likely resulted in the clinical signs of renal failure.

Simple carcinomas are the most common malignant mammary tumor in the dog⁵, and these tumors commonly spread by lymphogenous and hematogenous routes. Histologically, neoplastic epithelial cells (which were similar to those seen in the mammary tumor) were seen infiltrating every tissue examined in this case, including the multilobular tumor of bone presented here.

AFIP Diagnosis: Mandible (per contributor): Carcinoma with vascular invasion, and associated chondro-osseous and fibrous proliferation (fracture callus) Staffordshire Bull Terrier, canine.

Conference Comment: This case is a descriptive challenge. Sections contain at least two separate nodules expanding the submucosa of gingival epithelium. One nodule contains numerous islands of neoplastic epithelial cells; whereas, the other contains anastomosing bands of fibrous perichondrium which forms islands of well differentiated hyaline cartilage, several foci of chondrus to osseous metaplasia and, infrequently, areas of endochondral ossification.

Conference attendees agreed that the islands of neoplastic epithelial cells most likely represent metastasis from a primary carcinoma. Discussion focused on the bony, cartilaginous and fibrous nodule. Some felt this component of the lesion most likely represented a multilobular tumor of bone; others felt it was more representative of a callus formed in response to a pathologic fracture of the mandible.

Histologically, multilobular tumor of bone appears as a multilobular mass with lobules demarcated by fibrovascular septae and arranged in a characteristic trilaminar pattern consisting of a central area of cartilage or bone that may be calcified or ossified; a middle zone of plump, spindle-to ovoid-shaped cells; and a peripheral zone of fibrous tissue (1). The debate hinges on the lack of a prominent middle zone, also known as a cambium layer, surrounding the islands of cartilage and bone. Additionally, multilobular tumors are described as having a characteristic pattern of numerous contiguous lobules bordered by thin septae of spindle cell mesenchyme (5). It was noted that in our case the lobules were not contiguous

and that they are uncharacteristically large and separate from each other, more suggestive of reactive callus formation than multilobular tumor of bone. Regardless, the contributor provides an excellent review of multilobular tumor of bone and an interesting lesion guaranteed to spark much discussion.

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CASE IV – 05-2007 (AFIP 2984970)

Signalment: Female Great Dane, 15 weeks, canine

History: The dog presented with a 3 day history of generalized pain, reluctance to walk followed by lateral recumbency. Clinically the dog was tachycardic, anorexic and pyrexic. It went into cardiopulmonary arrest and did not respond to resuscitation.

Gross Pathology: The specimen is a puppy in good body condition and fair post mortem condition. The thorax contained approximately 35 cc of serosanguineous fluid. Approximately 60% of the lungs were mottled red and pink and oozed mucopurulent material when squeezed. There was a 1 mm space with white exudate between the metaphysis and physis of the humeri and femurs. In these bones the epiphysis and physis were easily separated from the metaphysis. The stool in the colon was soft and unformed. A moderate number of ascarids were

present within the intestines. Multiple areas of the small intestinal mucosa ranging from 5 to 10 mm in diameter were red.

Laboratory Results: ALP 281 IU/L (range 10-150), Phosphorus 7.6 mg/dl (range 2.1-6.3), Calcium 11.6 mg/dl (range 8.2-12.4), Band neutrophils 1188/uL (range 0-300), Segmented neutrophils 5544 (range 3,000-11,500)

Histopathologic Description: Specimen is epiphysis, physis and metaphysis. There is neutrophilic inflammation with necrosis of the underlying tissue and inflammatory cells (necrosuppurative osteomyelitis) that is most intense in the region of the primary trabeculae. Viable osteoblasts are not present and presumed to have undergone liquefactive necrosis. Viable osteoclast-like cells are present in the exudates. The cartilage cores in this region have only slight amounts of osteoid on their surfaces and many are fractured or missing (liquefactive necrosis/osteoclastic osteolysis). Fibrinoid vascular necrosis with necrosuppurative and fibrinous inflammation in the adjacent marrow/periosteum involve vessels deeper in the metaphysis, periosteum and within the epiphysis near the physis.

Contributor's Morphologic Diagnosis: Acute necrosuppurative metaphysitis with metaphyseal infarctions and acute fibrinoid vascular necrosis.

Contributor's Comment: The histologic lesions are characteristic of canine hypertrophic osteodystrophy (HOD). Lesions of hypertrophic osteodystrophy are found in long bones, most often the radius, ulna and tibia of young large-breed dogs (1-5). The primary lesions in HOD appear to be osteoblast and osteoclast necrosis, hemorrhage and neutrophilic inflammation where primary trabeculae would form leaving "naked" apparently elongated and retained calcified cartilage (1-5). This area appears as a radiodense region. Beneath this zone trabeculae are fractured and undergo marked osteoclastic resorption with marked suppurative inflammation (1-5). This area is seen as a radiolucent region. Later stages involve the formation of woven bone on the periosteum adjacent to the affected site and the replacement of reabsorbed trabecular bone with fibrous tissue (1-5). There has also been documentation of mineralization of soft tissues and vessels in some cases (1,2,4,5). Venous thrombosis in the diaphysis has been documented; however vasculitis has not (4). The pathogenesis is not completely understood, but possibilities include vaccine induced or bacterial or viral agents, although the lesions appear to be sterile in nature (1-5). Patients are presented with a reluctance to walk from the extreme pain caused by inflammation, necrosis and fractures (1-5). This pain eventually leads to the anorexia, depression, and weight-loss (1-5). Other clinical findings include a decrease in total protein and albumin, an increase in AP and high and imbalanced calcium and phosphorus levels (1-5). The high levels of calcium and phosphorus may be the result of bone resorption

and may lead to the soft tissue mineralization (5). Prognosis is good as the disease is self-limiting.

In the current case, the line of infraction has resulted in marked separation of the physis from the metaphysis in many histologic sections. This is an artifact of processing. This fracture space was visible grossly, but it was less than 1 mm wide. The cause of the widespread acute fibrinoid vasculitis in the bone is not apparent but suggests an Arthus reaction in the absence of visible infectious agents. Soft tissue mineralization was present in renal tubules, renal arteries, myocardium, and smooth muscle in the lung. The clinically reported cardiopulmonary arrest was suspected to be due to marked acute mucopurulent bronchopneumonia from which *Bordetella bronchiseptica* was cultured.

AFIP Diagnosis: Long bone: Osteomyelitis, necrosuppurative, acute, diffuse, severe, with microfractures and acute fibrinoid vascular necrosis, Great Dane, canine.

Conference Comment: The contributor provides an excellent review of hypertrophic osteodystrophy (HOD). Conference attendees discussed the neutrophilic inflammation and necrosis as most intense in the region of the primary trabeculae with a lesser amount present in the periosteum. There is a paucity of osteoid on the surface of the cartilage cores and many are either fractured or missing.

The name, hypertrophic osteodystrophy, comes from chronically affected cases where dogs may develop a markedly thickened metaphysis, widened periosteum, and deposition of extraperiosteal bone and cartilage; all of which are recognized clinically as painful, swollen joints.

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