

The Armed Forces Institute of Pathology
Department of Veterinary Pathology
Wednesday Slide Conference
2010-2011
Conference 18
9 February 2011

Conference Moderator:

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CASE I: 10L10D / 10L10C (AFIP 3164833).

Signalment: 9-month-old, female, Sprague-Dawley, rat (*Rattus norvegicus*).

History: This young female rat was part of an institutional breeding colony. She was euthanized due to the presence of a large mandibular mass.

Gross Pathology: The left mandible was surrounded and expanded to approximately 2cm in width by a highly infiltrative mass. The mass extended beyond the rostral aspect of the mandible and the overlying epithelium was ulcerated. On cut surface, tissue near the oral cavity was tan and friable while the deeper aspects were hard and gritty. All other organs and tissues were unremarkable.

Histopathologic Description: Mandible, left: Native tissue is extensively effaced by a well-demarcated, non-encapsulated and highly-infiltrative mass of neoplastic epithelial cells arranged in islands and anastomosing cords and trabeculae. Peripherally the neoplastic foci have a prominent layer of tightly packed tall-columnar cells with apically-located oval nuclei and prominent basilar cytoplasmic clearing. Centrally, neoplastic foci are comprised of cells that vary from stellate with long intercellular bridges to fusiform cells that are densely packed with prominent streaming and occasional whorls. The mitotic rate within the palisading layer is high with 1-5 per high power field and there are numerous scattered individual apoptotic cells. Along the basilar aspects of the palisading columnar cells are streams of fusiform cells often separated from the epithelial cells by variably thick seams and wedge-shaped foci of homogeneous eosinophilic extracellular matrix material. Matrix material frequently contains individual polygonal to fusiform cells within lacunae and is associated with a shift in appearance of the adjacent mesenchymal cells from fusiform to plump cuboidal or short columnar. There is multifocal ulceration of the oral epithelium and extensive necrosis of the subjacent tissue with loss of cellular detail and replacement by abundant viable and degenerate neutrophils, macrophages and fewer lymphocytes admixed with necrotic bone fragments, cellular and karyorrhectic debris, basophilic granular material (mineral), plant material and myriad colonies of coccoid bacteria.

Contributor's Morphologic Diagnosis: Mandible, left: odontoameloblastoma

Contributor's Comment: Odontoameloblastoma is an uncommon oral neoplasm with three distinct features: odontogenic epithelium, odontogenic ectomesenchyme and induction of mineralized dental tissues.¹¹ Odontogenic epithelium is characterized by peripheral palisading columnar cells with apically located nuclei and basilar cytoplasmic clearing, and central cells connected by long intercellular bridges that resemble the stellate reticulum.² Odontoameloblastomas commonly arise in the mandible, are locally aggressive and infiltrative, but do not metastasize.¹

Much of the odontogenic epithelial component of the neoplasm in the present case is consistent with the follicular variant of ameloblastoma; however, by definition, ameloblastomas are non-inductive neoplasms.^{1,8} During odontogenesis, ameloblasts degrade their basement membrane, achieve cell-to-cell contact with odontoblasts, and through their interaction induce the production of dentin.¹² In the neoplasm described in this report, periodic acid-Schiff reaction revealed a locally extensive loss of basement membrane associated with foci of eosinophilic matrix material representative of such induction. The histologic appearance of the eosinophilic matrix material and its presence adjacent to foci of odontogenic epithelium is most consistent with osteodentin, a tertiary form of dentin

with few recognizable dentin tubules that is rapidly produced and often entraps odontoblasts giving it a morphologic appearance similar to bone.^{6,7} Thus, as in the present case, a predominantly ameloblastic neoplasm with the additional features of odontogenic ectomesenchyme and induction of mineralized dental tissues warrants the diagnosis of odontoameloblastoma.^{8,11}

Previous histologic classification schemes for odontogenic neoplasms in domestic animals have referred to lesions with features similar to odontoameloblastoma as ameloblastic odontomas^{4,12} and the World Health Organization (WHO) classification of rodent tumors lists the two terms as synonymous;¹ however, the 1992 WHO classification of odontogenic neoplasms⁸ does not include ameloblastic odontoma as a recognized tumor classification and thus favors use of the term odontoameloblastoma. In a review of the nomenclature of odontogenic tumors in animals,³ the author also suggests that the term ameloblastic odontoma no longer be used and that the clinical behavior implied by the terms ameloblastoma (invasive) and odontoma (non-invasive) be considered when incorporating these terms into a diagnosis. Accordingly, the term odontoameloblastoma seems most consistent with the invasive nature of these lesions.

When the inductive component consists of mature tooth structures, the diagnosis of odontoameloblastoma is straightforward; however, the presence of thin seams of atubular dentin or osteodentin should not be overlooked as evidence of induction by odontogenic neoplasms and support the diagnosis of odontoameloblastoma over ameloblastoma.

AFIP Diagnosis: Mandible, left: Ameloblastic odontoma (odontoameloblastoma).

Conference Comment: Conference participants discussed the nomenclature of this tumor. With many neoplasms the nomenclature varies based on the classification system used. The most recent edition of the WHO *Histological Classification of Tumors of the Alimentary System of Domestic Animals* describes neither odontoameloblastoma nor ameloblastic odontoma.⁵ The authors do, however, describe an ameloblastic fibro-odontoma characterized by collagen-poor stroma reminiscent of dental pulp, interconnected cords and sheets of odontogenic epithelium, and advanced dentinal differentiation with deposition of enamel or dentin matrix. This description appears to have the features of an odontoameloblastoma. The Standardized System of Nomenclature and Diagnostic Criteria (SSNDC) Guide for lesions in the rat refers to this tumor as an ameloblastic odontoma (odontoameloblastoma).¹⁰

Odontogenic tumors are often difficult to describe and diagnose for many veterinary pathology residents. They are broadly categorized as epithelial (non-inductive) or epithelial with mesenchyme (inductive). Developing an algorithm is a helpful tool when evaluating odontogenic neoplasms. The following chart summarizes diagnostic criteria for histologically classifying odontogenic neoplasms in several veterinary species:^{2,5}

Tumor	OE*	Stroma	Mesenchyme	Matrix	Species Affected	Biological Behavior	Miscellaneous
Ameloblastoma	Yes	Not essential for diagnosis	None	None	Dog, cat, equine	Progressive; non-metastatic	

Amyloid-producing odontogenic tumor	Yes	Not essential for diagnosis	None	None	Dog, cat	Progressive; non-metastatic	Extracellular discrete round nodules of amyloid
Canine acanthomatous ameloblastoma	Yes	Stellate fibroblasts in dense collagen; regularly spaced dilated, empty blood vessels	Periodontal ligament	None	Dog	Locally aggressive; non-metastatic	Interconnected sheets of odontogenic epithelium
Ameloblastic fibroma	Yes	Loose, collagen poor, resembles dental pulp	Dental pulp	None	Young animals, cattle	Locally destructive; non-metastatic	Most common oral neoplasm in cattle
Ameloblastic fibro-odontoma	Yes	Loose, collagen poor; resembles dental pulp	Dental pulp	Dentin or enamel		Locally destructive; non-metastatic	
Complex odontoma	Yes	Well-differentiated dentinal tissue	Dental pulp	Dentin, enamel (may be mineralized)	Dog, rodent, primates, horse	Locally destructive; non-metastatic	Horse, rodents produce cementum; "balls of disorganized dental hard substance"
Compound odontoma	Yes	Well-differentiated dentinal tissue; dense collagen and vascular connective tissue	Dental pulp	Dentin, mineralized enamel	Young dogs	Locally destructive; non-metastatic	Multiple tooth-like structures (denticles)

*OE – odontogenic epithelium

Several participants observed fragments of food and few hair shafts associated with degenerate neutrophils within the gingival sulcus in some histologic sections from this rat. Dialogue surrounding the most likely predisposing factor for this ancillary finding, i.e. the oral neoplasm, and the possible pathologic sequelae led to discussion of a recent publication concerning the proposed etiopathogenesis of botryomycosis in mice.⁹ In the subject paper the author elegantly demonstrates that many mandibulofacial and maxillofacial abscesses likely result from fragmented hair shafts that become embedded in the gingival sulci of barbering animals leading to coagulase-positive *Staphylococcus aureus* infection.

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References:

1. Deschl U, Ernst H, Frantz J, et al. Digestive system. In: Mohr U, ed. *International Classification of Rodent Tumours*. Part I: The rat, 10. Lyon, France: International Agency for Research on Cancer; 1997:9.
2. Dubielzig RR. Odontogenic tumors and cysts. In: Meuten DJ, ed. *Tumors in Domestic Animals*. 4th ed. Ames, IA: Iowa State University Press; 2002:402.
3. Gardner DG. An orderly approach to the study of odontogenic tumours in animals. *J Comp Pathol*. 1992;107:427-438.
4. Gorlin RJ, Chaudhry AP, Pindborg JJ. Odontogenic tumors. Classification, histopathology, and clinical behavior in man and domesticated animals. *Cancer*. 1961;14:73-101.
5. Head KW, Cull JJ, Dubielzig RR, et al. *Histological Classification Tumors of the Alimentary System of Domestic Animals, 2nd series*. Vol. X. Washington DC: Armed Forces Institute of Pathology; 2007:47-52.

6. Holmstedt JO, McClugage SG, Clark JS, Guevara MJ. Osteodentin formation in continuously erupting teeth of guinea pigs. *J Dent Res.* 1977;56:1569-1576.
7. Karim AC, Eddy EL. A light and electron microscopic study of osteodentin formation in the rat incisor after adriamycin administration. *Am J Anat.* 1984;169:207-219.
8. Kramer I, Pindborg J, Shear M. *International Histological Classification of Tumours: Histological Typing of Odontogenic Tumours.* 2nd ed. Heidelberg, Germany: Springer-Verlag; 1992.
9. Lawson, GW. Etiopathogenesis of mandibulofacial and maxillofacial abscesses in mice. *Comp Med.* 2010;60:200-204.
10. Long PH, Leininger JR, Nold JB, Lieuallen WG. Proliferative lesions of bone, cartilage, tooth and synovium in rats. In: *Guides for Toxicologic Pathology.* Washington, DC: STP/SRP/AFIP; 1993:6-7.
11. Mosqueda-Taylor A, Carlos-Bregni R, Ramírez-Amador V, Palma-Guzmán JM, Esquivel-Bonilla D, Hernández-Rojase LA. Odontoameloblastoma. Clinico-pathologic study of three cases and critical review of the literature. *Oral Oncol.* 2002;38:800-805.
12. Walsh KM, Denholm LJ, Cooper BJ. Epithelial odontogenic tumours in domestic animals. *J Comp Pathol.* 1987;97:503-521.

CASE II: 10L11 A / J (AFIP 3164879).

Signalment: 12-month-old, male, C57/Bl6 10ScSn-Dmd mdx/J, mouse (*Mus musculus*).

History: A subcutaneous mass was present in the lumbar region. The mouse was euthanized by CO₂.

Gross Pathology: A firm, non-movable subcutaneous mass (1.2 cm x 1.8 cm x 1.5 cm) was present in the lumbar region. The mass was cream colored on cut surface.

Histopathologic Description: Tissue: Mass from lumbar region: Effacing and replacing approximately 80% of the epaxial musculature, and extending from the dorsal muscle surface to the dorsal aspect of the underlying vertebra, is a poorly-demarcated, non-encapsulated, infiltrative neoplastic mass consisting of tightly-packed neoplastic cells arranged in haphazard bundles and streams supported on a fine fibrovascular stroma. Neoplastic cells are polygonal to spindloid, with indistinct margins and abundant finely fibrillar basophilic cytoplasm. Nuclei are oval to crimped with coarsely stippled chromatin and 0-1 visible magenta nucleoli. Anisocytosis and anisokaryosis are marked and mitoses are too numerous to count and frequently bizarre. Nuclear rowing is evident, and scattered plump multinucleated neoplastic cells are present. Along the periphery of the primary mass, neoplastic cells dissect between and multifocally surround and separate native myofibers. Adjacent to the mass, multifocal myofibers contain hypereosinophilic and condensed globular sarcoplasm (degeneration), with variable loss of nuclear detail (necrosis). Multifocal myofibers are small in diameter and contain basophilic sarcoplasm and multiple internal nuclei (regenerative), or contain eosinophilic sarcoplasm and central nuclei (post-regeneration). Myofiber diameter is highly variable, and multifocal small-diameter fibers are surrounded by populations of polygonal cells (proliferating myoblasts).

Contributor's Morphologic Diagnosis: (1) Mass within lumbar epaxial muscle: Rhabdomyosarcoma. (2) Skeletal muscle: Myofiber degeneration, necrosis and regeneration, moderate, diffuse, chronic, with myoblast proliferation.

Contributor's Comment: The heritable, X-linked true muscular dystrophies are the result of defects in the gene encoding the dystrophin protein, and have been described in the dog, cat, mouse, and human.⁹ Dystrophin is a cytoplasmic protein expressed in skeletal, cardiac and smooth muscle which as part of the dystrophin-dystroglycan-laminin complex links the myofibrillar actin cytoskeleton to the extracellular matrix and is required for sarcolemmal stability.¹⁰ Absence or defects within the dystrophin protein contribute to contraction-associated myofiber necrosis and regeneration, with progressive muscle weakness and eventual replacement of muscle by fibrotic and adipose tissue in humans. Affected boys usually die early within the second decade of life due to respiratory or cardiac failure.^{2,10} The mouse model of Duchenne's muscular dystrophy (mdx) arose in 1976 as an X-linked spontaneous dystrophin mutation in a colony of C57/Bl10 mice,¹ and has been extensively utilized in pathogenesis and

therapeutic studies. Mice with dystrophin defects experience the onset of myofiber degeneration at 3-5 weeks of age, similar to the juvenile onset of clinical signs in humans, and cardiac and diaphragmatic dysfunction likely contribute to a reduced life span compared to wild-type mice. However, unlike the analogous human disease, mdx mice follow a milder clinical course in that limb myofiber regeneration and hypertrophy continue well into adulthood, albeit with a decrease in muscle strength.² Histological features of muscular dystrophy include a variation in fiber diameter in that the muscle tissue is comprised of a mosaic of hypertrophied, degenerating and regenerating myofibers. The presence of multinucleated myofibers and fibers with central nuclei are evidence of the regenerative process.

Rhabdomyosarcoma, otherwise rare in other strains of laboratory mice, has been identified as a common spontaneous tumor in aged mice lacking functional dystrophin or alpha-sarcoglycan.^{2,4} In a previous longevity study involving 94 mdx mice, six animals developed rhabdomyosarcomas between 16.5 and 24 months of age, whereas no rhabdomyosarcomas were noted in 83 age-matched wild-type background strain (C57BL/10ScSn/J) mice.² The mouse in the present case was one of 71 mdx mice housed at the Iowa State University College of Veterinary Medicine, two others of whom developed rhabdomyosarcomas between February 2010 and May 2010. The tumor in the present case was positive for desmin upon immunohistochemical analysis, confirming the diagnosis.³ The pathogenesis of this entity is unknown, but it is postulated that the continual proliferation of the satellite cell pool, which accompanies the degeneration and regeneration of myofibers, lends itself to random mutations and neoplastic transformation.² Early exhaustion of this satellite cell pool in human muscular dystrophy is likely the reason that rhabdomyosarcoma is uncommonly reported in human patients.²

Additional changes in this mouse included myocardiocyte loss and replacement by plump fibroblasts and wispy collagen (fibrosis), and the presence of regenerative muscle fibers in the diaphragm.

AFIP Diagnosis: 1. Skeletal muscle, epaxial: Rhabdomyosarcoma.
2. Skeletal muscle: Myocyte degeneration, necrosis, and atrophy, diffuse, moderate, with myocyte regeneration.
3. Bone, vertebrae, ilium, and femur; intervertebral disk; and spinal cord: Essentially normal tissue (not present in all sections).

Conference Comment: Conference participants readily diagnosed the sarcoma as a rhabdomyosarcoma and discussed immunohistochemical stains used to differentiate tumors of muscle origin. Vimentin, desmin, muscle specific actin and myoglobin are commonly used immunomarkers for rhabdomyosarcoma.¹¹ Many embryonal or primitive muscle tumors may be immunohistochemically negative for myoglobin since it is expressed late in myocyte development.¹¹ Myogenin and Myo-D1 can be used for primitive skeletal muscle sarcomas and have shown some success in diagnosing rhabdomyosarcomas in dogs.^{5,7} These markers are transcription factors in the nuclei of developing myocytes, and therefore exhibit positive nuclear immunoreactivity; however, interpretation of Myo-D1 must be done with care, as there is frequent cytoplasmic staining.¹¹ There has been recent interest in using Pax7 for the diagnosing of primitive rhabdomyosarcoma. The Pax7 protein is a transcription factor expressed in activated and quiescent skeletal muscle satellite cells which acts to regulate their survival and specification.⁸ There is intense research in isolating and characterizing satellite cells, not only to determine their role in neoplasia, but also in treating degenerative diseases of skeletal muscle.⁸

Few participants diagnosed the skeletal muscle degeneration, necrosis and regeneration occurring away from the neoplasm. Once more clinical information was provided, such as the phenotype of the mouse and its research utilization, they readily identified areas of myocyte change. Research findings support the role of satellite cells as skeletal muscle stem cells.⁸ After skeletal muscle damage, there is active Notch signaling due to upregulation of delta-like ligands on satellite cells causing them to proliferate, which is evident histologically as a round, plump appearance.⁶ Inflammatory cells secreting insulin-like growth factor (IGF)-1, platelet-derived growth factor (PDGF) and IL-6 also promote satellite cell and myoblast proliferation and differentiation.⁶ Regenerative changes in skeletal muscle are characterized by sarcolemmal basophilia, central alignment of many nuclei (i.e. nuclear rowing) and vesiculate nuclei.¹²

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References:

1. Bulfield G, Siller WG, Wight PAL, Moore KJ. X chromosome-linked muscular dystrophy (mdx) in the mouse. *Proc Natl Acad Sci.* 1984;81:1189-1192.
2. Chamberlain JS, Metzger J, Reyes M, Townsend D, Faulkner JA. Dystrophin-deficient mdx mice display a reduced life span and are susceptible to spontaneous rhabdomyosarcoma. *FASEB J.* 2007;21:195-204.
3. Cooper BJ, Valentine BA. Tumors of muscle. In: Meuten DJ, ed. *Tumors in Domestic Animals*. 4th ed. Ames, IA: Iowa State Press; 2002:319-363.
4. Fernandez K, Serinagaoglu Y, Hammond S, Martin LT, Martin PT. Mice lacking dystrophin or alpha sarcoglycan spontaneously develop embryonal rhabdomyosarcoma with cancer-associated p53 mutations and alternatively spliced or mutant Mdm2 transcripts. *Am J Pathol.* 2010;176:416-434.
5. Kobayashi M, Sakai H, Hirata A, et al. Expression of myogenic regulating factors, myogenin and MyoD, in two canine botryoid rhabdomyosarcomas. *Vet Pathol.* 2004;41:275-277.
6. Kumar V, Abbas AK, Fausto N, Aster JC. Tissue renewal, regeneration and repair. In: Kumar V, Abbas AK, Fausto N, Aster JC, eds. *Robbins and Cotran Pathologic Basis of Disease*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2009:85-86.
7. Murakami M, Sakai H, Iwatani N, et al. Cytologic, histologic and immunohistochemical features of maxillofacial alveolar rhabdomyosarcoma in a juvenile dog. *Vet Clin Pathol.* 2010;39:113-118.
8. Tedesco FS, Dellvalle A, Diaz-Manera J, Messina G, Cossu G. Repairing skeletal muscle: regenerative potential of skeletal muscle stem cells. *J Clin Invest.* 2010;120:11-19.
9. VanVleet JF, Valentine BA. Muscle and tendon. In: Maxie MG, ed. *Pathology of Domestic Animals*, 5th ed. Vol. 1. Philadelphia, PA: Elsevier Saunders; 2007:185-280.
10. Watchko JF, O'Day TL, Hoffman EP. Functional characteristics of dystrophic skeletal muscle: insights from animal models. *J Appl Physiol.* 2002; 93:407-417.
11. Wick MR, Hornick JL. Immunohistopathology of soft tissue and osseous neoplasms. In: Dabbs DJ, ed. *Diagnostic Immunohistochemistry: Theranostic and Genomic Applications*. Philadelphia, PA: Saunders Elsevier; 2010:91-92.
12. Van Vleet JF, Valentine BA. Muscle and tendon. In: Maxie MG, ed. *Jubb, Kennedy and Palmer's Pathology of Domestic Animals*. Vol. 1, 5th ed. Philadelphia, PA: Elsevier Ltd; 2007:200-201.

CASE III: 15147-3B-3T (AFIP 3166458).

Signalment: 5-6-month-old, female intact, landrace X large white cross-bred, porcine (*Sus domesticus*).

History: A large number of 5- to 6-month-old replacement gilts were transported by truck over a 300-mile distance. The gilts were reported to have walked normally prior to being transported but an “unacceptable” number of them were severely lame after arrival, with the lameness being localized to one or both elbow joints. Humeri from a subset of the affected animals were sent to the Minnesota Veterinary Diagnostic Laboratory for determination of the cause of the lameness. The histologic section is from the distal humerus of one of the affected pigs.

Gross Pathology: The articular cartilage of the trochlea (right) contains a locally extensive, thickened area involving approximately 75% of the articular surface. The axial margin of this thickened area exhibits clefting and flap formation. Most of the thickened area of cartilage remains intact; however, there is an area of loss of articular cartilage (approximately 15% of the total cartilage) in the axial aspect of the trochlea, with exposure of the subchondral bone (ulceration). The cartilage of the sagittal ridge (central area of joint surface) also is focally extensively ulcerated and thickened. Radiographs of the serially sectioned distal humerus (2-3 mm slab sections) demonstrate well-demarcated, locally extensive areas of lucency in the subchondral bone of the trochlea and sagittal ridge. A higher magnification image of one of these slabs demonstrates nearly complete loss of radiodensity in these areas; the trochlea is on the right side of the image.

Histopathologic Description: **Bone:** The slide is composed of one coronal section of the distal humeral trochlea. The articular-epiphyseal complex in the abaxial 2/3 of the trochlea is variably thickened, and contains a longitudinal cleft separating the cartilage from the underlying subchondral bone. Subjacent to this cleft is an extensive area of myelofibrosis and loss of bone trabeculae. Focally, in the axial aspect of the trochlea, the cartilage cleft reaches the articular surface. This area of articular cartilage exhibits fibrillation, areas of chondrocyte necrosis, and numerous chondrocyte clones (chondrones). Along the deep surface of the cleft is a variably thin zone of necrotic cartilage characterized by pale, eosinophilic matrix containing low numbers of eosinophilic chondrocytes that contain no discernible nuclei. The viable cartilage immediately adjacent to the zone of necrosis contains numerous chondrocyte clones (chondrones). Subjacent to the cartilage flap is a thick mat of eosinophilic, fibrillar material (fibrin). Underlying this mat of fibrin is well vascularized fibrous connective tissue (granulation tissue), denser fibrous

connective tissue (fibrosis), and foci of chondro-osseous tissue and woven bone replacing the subchondral bone (myelofibrosis). This tissue extends a variable distance into the marrow spaces of the underlying epiphyseal bone. There is localized osteopenia secondary to the decreased overall bone density in the affected area that is clearly visible in the associated radiographs. Fragments of bone trabeculae immediately subjacent to the cleft contain margins lined by active osteoblasts and by osteoclasts within erosion lacunae (osteoclastic resorption). The cartilage at the extreme axial aspect of the joint contains moderate numbers of chondrocyte clones (chondrones) and several foci of neovascularization.

Contributor's Morphologic Diagnosis: Articular-epiphyseal cartilage complex, chronic, locally extensive chondronecrosis with intralesional clefting, failure of endochondral ossification, and myelofibrosis

Contributor's Name of the Disease: Osteochondrosis *dissecans*

Contributor's Comment: Osteochondrosis is a focal or multifocal disturbance of endochondral ossification in which growth cartilage fails to undergo matrix calcification or vascular invasion and is not converted to bone.³ Osteochondrosis affects multiple animal species, most commonly pigs, horses, and dogs.² This condition has a multifactorial etiology, with anatomic conformation and heredity^{1,5} being the causes that are supported most commonly by the scientific literature. Studies of the early lesions in horses and swine have reported that failure of blood supply to the growth cartilage leads to cartilage necrosis, resulting in failure of this tissue to undergo matrix calcification or vascular invasion.^{1,4}

Osteochondrosis can be classified as *latens* (lesion confined to epiphyseal cartilage), *manifesta* (lesion accompanied by delay in endochondral ossification), and *dissecans* (cleft formation through articular cartilage) to designate the stage of the disease process.¹ In the present case, "trauma" occurring during transportation most likely caused the conversion of *manifesta* lesions to *dissecans* lesions, resulting in clinical lameness in animals that appeared to be sound prior to transportation. In this chronic stage of the disease, necrotic blood vessels within the epiphyseal cartilage are no longer present.

Participants are encouraged to review Wednesday Slide Conference 2008-2009; conference 21; case #1 which presents an acute case of osteochondrosis *latens* and *manifesta* in a 6 week-old foal, whereas the present case is an example of chronic lesions of osteochondrosis *dissecans*.

AFIP Diagnosis: Long bone, distal humeral trochlea and articular-epiphyseal complex (per contributor): Chondronecrosis, chronic, focally extensive, with subchondral clefting, osteopenia, myelofibrosis and failure of endochondral ossification.

Conference Comment: As noted by the contributor, there are various classifications of osteochondrosis based on the histomorphologic appearance, which frequently correlates with lesion chronicity. In discussing the progression of osteochondrosis, the moderator commented that the four characteristics of chronic OCD include chondronecrosis, clefting, myelofibrosis and subchondral bone changes. Conference participants commented on excellent quality of the tissue sections and slide preparation and the classic histopathologic appearance of this lesion.

The predilection sites for development of osteochondrosis *dissecans* vary by species. The clinical information, including the description of the affected joints, is typically more useful for the clinician and radiologist; however, pathologists should be familiar with these sites in order to assess the locations for possible lesions at necropsy.²

- Pig: Joint surfaces of medial humeral and femoral condyles; anconeal process; lumbar vertebrae; mediolateral talus; humeral head; glenoid cavity of the scapula; distal ulna; and dorsal acetabulum
- Dog: Caudal aspect of the humeral head (most common); medial aspect of the humeral condyle; lateral and medial femoral condyle(s); and medial trochlear ridge of the tibial tarsal bone
- Horse: Lateral trochlear ridge; medial femoral condyle; patella; dorsal edge of the sagittal ridge of the distal tibia; and various sites in the tarsal and fetlock joints
- Cattle: Lateral trochlear ridge; humeral head; distal radius; elbow joint; and tibial tarsal and occipital condyles

Several conference participants preferred the diagnosis of chondrodysplasia. As noted by the contributor the pathogenesis of osteochondrosis *dissecans* is due to disturbance of endochondral ossification, whereas the underlying pathogenesis of chondrodysplastic diseases is attributed to defects in cartilage formation. The contributor provides an excellent description of the key histologic features of osteochondrosis *dissecans*. In

contrast, the histologic lesions of chondrodysplasia are typified by unevenness in the physal growth plate, nodular hypertrophy of the growth cartilage with multiple small centers of ossification, an increased width of the zones of chondrocyte proliferation and hypertrophy, and failure to form or maintain orderly chondrocyte columns. Clinically, chondrodysplastic lesions typically affect bones which undergo endochondral ossification resulting in various forms of dwarfism. Examples of chondrodysplastic diseases in domestic animals include the following:²

- Cattle: Bulldog type, Telemark lethal, brachycephalic (“snorter) type and long-headed type
- Sheep: Spider lamb syndrome
- Canine: Chondrodysplasia has been described in Alaskan malamute, Norwegian elkhound, English pointer, Great Pyrenees, miniature poodle, beagles, Scottish deerhound and Labrador retrievers.
- Feline: Scottish fold

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References:

1. Olstad K, Ytrehus B, Ekman S, Carlson CS, Dolvik NI. Early lesions of osteochondrosis in the distal tibia of foals. *J Orthop Res.* 2007;8:1094-1105.
2. Thompson K. Diseases of bones and joints. In: Maxie MG, ed. *Jubb, Kennedy and Palmer's Pathology of Domestic Animals.* Vol. 1, 5th ed. Philadelphia, PA: Elsevier Ltd; 2007:25-33,136-145.
3. Ytrehus B, Carlson C S, Ekman S. Etiology and pathogenesis of osteochondrosis. *Vet Pathol.* 2007;4:429-448.
4. Ytrehus B, Carlson C S, Lundeheim N, et al. Vascularisation and osteochondrosis of the epiphyseal growth cartilage of the distal femur in pigs-development with age, growth rate, weight and joint shape. *Bone.* 2004;3:454-465.
5. Ytrehus B, Grindflek E, Teige J, et al. The effect of parentage on the prevalence, severity and location of lesions of osteochondrosis in swine. *J Vet Med A Physiol Pathol Clin Med.* 2004;4:188-195.

CASE IV: D09-23400 (AFIP 3166451).

Signalment: 1-day-old, female intact, Peruvian Paso, horse (*Equus caballus*).

History: Since birth, the foal had been unable to rise, had no suckle reflex, and had marked joint laxity. The foal was euthanized at four hours of age.

Laboratory Results: Aerobic cultures of the lung and liver yielded no growth. No *Salmonella spp.* was isolated from tissue pool. Samples of tissue homogenate were negative for equine herpes virus (EHV). A section of liver was submitted for heavy metal and mineral analysis and the results were within normal limits.

Gross Pathology: The entire body of a 32.4 kg intact female foal in good body condition presented for necropsy in an excellent state of postmortem preservation. The foal had a prominent convex nasal bone and marked mandibular brachygnathia inferior (1.5 cm excess over most rostral point on mandible). The placenta weighed 2.7 kg, was complete, and had a normal size, shape, color, and consistency.

The thyroid gland lobes were prominent, dark purple, evenly colored, and of normal shape and consistency.

Examination of longitudinal cut sections of femur and humerus revealed triangular-shaped areas of bone extending from the growth plate (base of triangle) into the metaphysis and diaphysis, filling the marrow cavity, and creating an hourglass appearance (also visible radiographically). Bones cut in transverse section had a lamellated appearance. There was excessive laxity of joints in the distal limbs (carpus/tarsus and distal) both ventrodorsally and laterally. The mouth could not be opened fully. All of the right ribs were fractured, except for ribs 1 and 4; at the site of each fracture, there was focal reddening of the adjacent subcutaneous tissues (hemorrhage). The left ribs 4, 5, 6, 7, 8, 10, 11, 14, 15, and 16 were similarly fractured. Many of the long bones were extremely fragile, breaking relatively readily on hand pressure.

Postmortem Faxitron radiographs of the skull, humerus, femur, tarsus, and carpus revealed a generalized increase in medullary bone opacity. Specifically, there were parallel linear columns of bone originating from the physal area and radiating toward the central diaphysis. These columns represented primary spongiosa and obliterated the

normal medullary cavity. These medullary opacities formed an hourglass appearance with the central area of the hourglass being the center of the affected bone.

Histopathologic Description: **Bone:** This is a longitudinal section of long bone metaphysis/diaphysis. The marrow cavity contains a large, wedge-shaped area that occupies approximately 50% of the total tissue area. The tissue in this area is composed of fine trabeculae of bone that exhibit marked retention of calcified cartilage cores (retained primary spongiosa). The outer surfaces of the bony spicules are often scalloped and contain moderate numbers of osteoclasts within erosion lacunae. Osteoblasts appear to be reduced in number and, when identified, are flattened (quiescent). The spaces between bone spicules contain small numbers of erythroid and myeloid precursors admixed with a small amount of loose fibrous connective tissue. The remaining bone trabeculae appear to be composed of woven bone and exhibit a moderate degree of osteoclastic bone resorption. The cortical bone is diffusely trabeculated.

Contributor's Morphologic Diagnosis: Long bone, metaphyseal and diaphyseal osteosclerosis, diffuse, severe, with cortical osteopenia.

Contributor's Comment: Osteopetrosis (or "marble bone disease") is part of a group of rare disorders characterized by defective osteoclastic bone resorption and the accumulation of primary spongiosa in marrow cavities. Osteopetrosis in Peruvian Pasos has been described previously;¹ however, the precise genetic mechanism has not yet been characterized. In humans, juvenile-onset osteopetrosis has an autosomal recessive inheritance pattern, and although the total number of cases is small, evidence to date suggests that the disease in Peruvian Paso horses also is inherited as an autosomal recessive trait.² In osteopetrosis, the bone resorptive function of osteoclasts is dysfunctional, leading to loss of normal bone turnover and retention of bone within central medullary cavities. Affected foals suffer many fractures. Since the medullary cavity is filled with retained primary spongiosa, the amount of bone marrow is diminished, leading to anemia and leukopenia. Although affected foals are of normal size at birth and are born alive, they are unable to stand, become lethargic, and are susceptible to infections. These animals are commonly euthanized within the first week of life.

AFIP Diagnosis: Long bone: Osteosclerosis, medullary, diffuse, marked, with retention of primary spongiosa, cortical osteopenia, and lack of marrow hematopoietic elements.

Conference Comment: Conference participants were intrigued by the cortical osteopenia and failed compaction of cortical bone, and they speculated on the relationship between cortical osteopenia and osteopetrosis. Osteopenia is a common concurrent finding in various forms of human osteopetrosis. A literature search failed to identify any publication explaining a possible pathogenetic mechanism for the simultaneous occurrence of osteopenia in the face of osteopetrosis. In fact, the last sentence of the abstract in a human case report of osteopetrosis identified during the literature review stated, "How osteopenia follows [osteopetrosis] is an enigma of human skeletal pathobiology."³ This situation appears to be seemingly true for veterinary medicine.

The histologic descriptions, interpretations, and diagnoses of bone lesions can be a daunting challenge for veterinary pathologists and training residents alike. The following chart provides a brief summary of some of the more classic bone diseases:²

Disease	Disease Process	Underlying Abnormality	Gross Features	Key Histologic Features
Chondrodysplasia	Abnormal development of ossification centers	Point mutation in the gene encoding FGFR3	Irregularly thickened physis; Roman-nosed; knock-kneed	Multiple ossification centers in nodules of hypertrophic cartilage; increased width of the proliferative and hypertrophic zones of the physis
Osteogenesis imperfecta	No osteoclastic resorption or realignment of trabeculae	Mutations in COL1A1/ COL1A2 genes → defect in type I collagen produced by OB	Brittle bones with normal shape; blue sclera; misshapen, pink teeth	Calcified cartilage spicules lined by thin layer of mineralized matrix & OB; woven, osteopenic cortical bone

Scurvy	Decrease/failure in collagen deposition resulting in failure of EO	Lack L-gulonolactone oxidase for ascorbic acid synthesis	Swollen joints; fractures; periosteal hemorrhages	Naked spicules of calcified cartilage ("scorbutic lattice"); sparse OB; infractions; thin physis
Rickets*	Failure of mineralization → defective osteoid mineralization & EO at physis	Decreased vitamin D ₃ or phosphorus	Enlarged costochondral junctions ("rachitic rosary"); focal thickening of physal cartilage; short, thickened diaphysis	Persistent hypertrophic chondrocytes; thick, irregular metaphyseal trabeculae with unmineralized osteoid; infractions
Fibrous Osteodystrophy	Increased bone resorption with replacement by fibrosis	Increased parathormone → functional parathyroid adenoma, 2° renal or 2° nutritional	Bilateral swelling of the skull, especially the mandible and maxilla	Increased OC bone resorption; fibroplasias; OBs producing woven bone; disorganized spicules of woven bone lacking cartilage core
Hypertrophic Osteopathy	Periosteal new bone formation	Chronic inflammation / neoplasia; botryoid rhabdo-myosarcoma (dog); ovarian tumors (horse)	Lesions start on the distal limbs and progress proximally	Early → edema, proliferation of vascularized connective tissue in the periosteum; Late → trabeculae of woven bone perpendicular to the cortex
Metaphyseal Osteopathy	Young, growing dogs; long bones but, not distal to carpus	Unknown	Bilaterally symmetrical swelling; sterile suppurative osteomyelitis	Persistence of calcified cartilage lattice of 1° spongiosa; neutrophilic inflammation, necrosis, infractions

* Disease in adults with the same lesions in the cortex

FGFR3: fibroblast growth factor receptor 3; COL1A1/2: type I collagen gene; EO: endochondral ossification; OB: osteoblasts; OC: osteoclasts

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References:

1. Berry C, House J, Poulos P, et al. Radiographic and pathologic features of osteopetrosis in two Peruvian Paso foals. *Can Vet J.* 1994;35:5, 355-361.
2. Thompson K. Diseases of bones and joints. In: Maxie MG, ed. *Jubb, Kennedy and Palmer's Pathology of Domestic Animals*. Vol. 1, 5th ed. Philadelphia, PA: Elsevier Ltd; 2007:25-40, 59, 57-88, 136-145.
3. Whyte MP, Wenkert D, McAlister WH et al. Dysosteosclerosis presents as an "osteoclast-poor" form of osteopetrosis: Comprehensive investigation of a 3-year-old girl and literature review. *J Bone Miner Res.* 2010;25:2527-2539.