



WEDNESDAY SLIDE CONFERENCE 2015-2016

Conference 9

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Dr. Julie Engiles, DVM, PhD, DACVP
Associate Professor, University of Pennsylvania
New Bolton Center, Kennett Square PA

CASE I: E305-08A (JPC 4001570).

Signalment: 23-month-old female
Corriedale sheep (*Ovis aries*).

History: The sheep was in good condition, but had been showing increasing reluctance to rise over the previous weeks. The front limbs were extremely bowed, and there was pronounced thoracic lordosis. This sheep was part of an embryo transfer trial using semen and ovum from sheep affected with suspected inherited rickets. The sheep were

on good quality pasture with high soil phosphorus levels.

Gross Pathology: On post-mortem examination there was segmental thickening of the distal radial physis, and enlargement of the costochondral junctions of ribs 5-10. The radius showed dorsal and valgus curvature. All the long bones had thickened cortices, and enthesiophytes were present around the carpal and tarsal joints.



Ribs, sheep. there was diffuse enlargement of the costochondral junction of ribs 5-10. (Photo courtesy of: Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Tennant Drive, Palmerston North, New Zealand)

Laboratory Results: Calcium 1.97 mmol/L (2.0-2.7)
Phosphate: 0.73 mmol/L (1.3-2.7)
25-hydroxyvitamin D₃: 36 nmol/L (no difference compared with control sheep)
1,25-dihydroxyvitamin D₃: 154 pmol/L (no difference compared with control sheep)

Histopathologic Description: The physal lesion is characterized by irregular segmental thickening of the hypertrophic zone and dis-



Ribs, sheep. Transverse sectioning of affected ribs demonstrate obvious irregularities within the growth plate with visible retention of cartilage cores extending into the flared metaphysis. (Photo courtesy of: Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Tennant Drive, Palmerston North, New Zealand)

organization of chondrocyte columns. Tongues and islands of persistent hypertrophic chondrocytes extend from the physis into the metaphysis. The cartilage matrix in some areas is eosinophilic and interspersed with fibrin. The metaphysis consists of thickened, disorganized trabeculae of woven bone, fibrous connective tissue, degenerate cartilage matrix, fibrin and hemorrhage merging into thick trabeculae of lamellar bone. In some sections osteoclastic resorption cavities are present in the cortex, and occasionally within trabeculae. Wide osteoid seams line some trabeculae.

Contributor's Morphologic Diagnosis:

Rib: Osteodystrophy with physal thickening and unmineralized osteoid seams.

Contributor's Comment: Rickets is a metabolic bone disease, most commonly due

to either phosphorus deficiency or vitamin D deficiency. The classical lesions of rickets include: Segmental thickening of growth plates (particularly of rapidly growing bones), enlargement of costochondral junctions (the so-called rachitic rosary), and spontaneous fractures.¹⁰ In cattle, pigs and sheep collapse of subchondral bone of the humeral head is also described. Impaired mineralization of the physis and newly formed osteoid leads to islands and tongues of hypertrophic chondrocytes extending into the metaphysis, disorganization of the primary spongiosa, thick osteoid seams lining trabeculae and microfractures.¹⁰

Rarely, rickets may be due to inherited defects in vitamin D metabolism or renal tubular function. See the recent review on



Radius, sheep. The growth plate of the distal radius is also segmentally expanded and there is a retained cartilage core extending toward the metaphysis. (Photo courtesy of: Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Tennant Drive, Palmerston North, New Zealand)

vitamin D metabolism and rickets for further details.⁴

In Corriedale sheep with autosomal recessive inherited rickets,^{3,5} a novel nonsense mutation in the non-collagenous bone protein, dentin matrix protein 1 (DMP1), leading to a premature stop codon and truncation of the protein has been found (personal communication, K. Dittmer). The equivalent form of this disease in humans is called autosomal recessive hypophosphataemic rickets I. The mutation in DMP1 leads to increased serum fibroblast growth factor 23 (FGF23) concentration. FGF23 inhibits the renal NPT-2a co-transporter (a Na-P co-transporter) and CYP27B1 (1 α -hydroxylase) activity in the kidney, altering phosphate reabsorption in the renal tubules, and inhibiting 1,25(OH)₂D₃ production. Consequently, humans with this condition have hypophosphataemia, phosphaturia, inappropriately normal serum 1,25(OH)₂D₃ concentrations and rickets.⁶

The thickened cortices seen in the long bones of affected sheep² and enthesiophytes are a feature of X-linked hypophosphataemic

rickets in humans.⁹ The pathogenesis of this is unclear. However in the sheep, we hypothesize that the enthesiophytes are the result of strain on ligament/tendon attachments to weakened, poorly mineralised bone. Likewise, the thickened cortices are a consequence of bone being deposited at sites of strain in order to decrease deformation associated with mechanical loading, as described by Wolff's law or the mechanostat model.^{7,8}

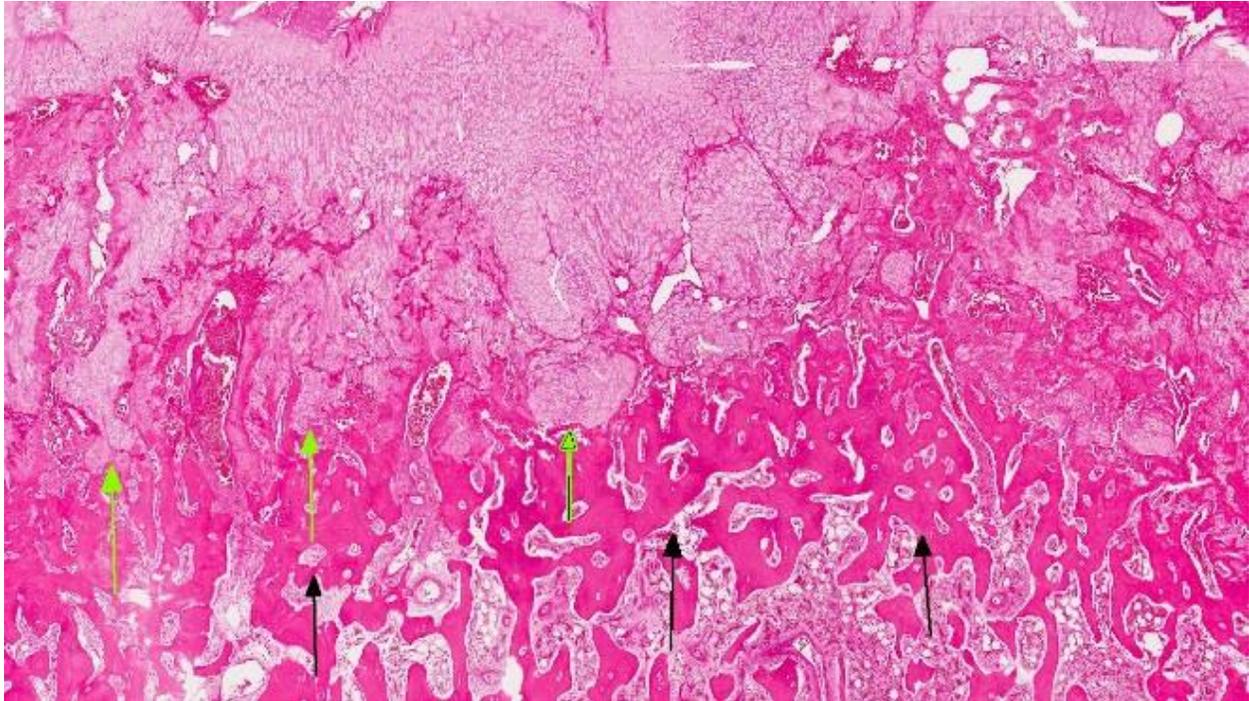
This inherited disease has the potential to be widespread in Corriedale sheep worldwide. A test for heterozygous animals has been developed.

JPC Diagnosis: Rib bone: Physeal chondrodysplasia, diffuse with excessive proliferation of the zone of hypertrophy, retained cartilage cores, lack of mineralization and myelofibrosis.

Conference Comment: The histologic description given in conference was very similar to the contributor's description. The absence of mineralized cartilage and decreased number of normal osteoclasts, along with the abnormal distribution of chondrocytes into disorganized clusters (rather than forming organized columns or rows) with scattered chondrocyte necrosis were also described and discussed. Some conference participants noted the presence of



Rib, sheep. Even at low magnification, long tongues of unremodeled cartilage are visible, extending from the growth plate into the metaphysis. (HE, 4X)



Rib, sheep. Failure of physal chondroclasis has resulted in retention of long, irregularly shaped cores of unmineralized, unremodeled cartilage (green arrows), as well as irregularly, often horizontally anastomosing trabeculae of primary spongiosa. (HE, 14X)

enthesiophytes at sites of tendon/ligament attachment, although this was not a feature present in all slides. This observation led to specific discussion of how enthesiophyte formation relates to the pathogenesis of inherited rickets, as addressed in the contributor's comment above.

The lesions of rickets result from failure of mineralization, which includes both impaired endochondral ossification and failed mineralization of osteoid. This results in the presence of excess osteoid as well as the prominent nodular thickenings of cartilage which are apparent grossly. The enlarged irregular physis is composed of increased numbers of disorganized chondrocytes, as seen in this case. The metaphyses are flared secondary to impaired osteoclast removal of cartilage and unmineralized bone (osteoid) from the cutback zones. Osteoclasts cannot bind unmineralized matrix, impairing remodeling and resulting in accumulation of

unmineralized osteoid and cartilage.¹ Naturally occurring rickets is uncommon in sheep, cattle, horses, dogs, and cats; llamas and alpacas are highly susceptible and pigs are susceptible when they don't receive adequate feed supplementation. There is also a genetic form in pigs which is similar to a condition that occurs in people.⁴ Like rickets, the pathogenesis of osteomalacia also involves defective mineralization, but is a condition that occurs in adult animals after the growth plates have closed and therefore does not involve growth plates. Osteomalacia results in increased amounts of unmineralized osteoid at sites of pressure or stress.

Vitamin D₃ is formed in the skin and can also be absorbed in the diet, as can vitamin D₂. It is stored in fat or transported to the liver where it must undergo the first step of activation, hydroxylation. Once hydroxylated in the liver, 25-hydroxycholecalciferol

[25(OH)D₃], which is the primary form of vitamin D in circulation, must again be hydroxylated in the kidney by 1 α -hydroxylase, to form 1, 25-dihydroxycholecalciferol [1,25(OH)₂D₃], the metabolically active form of vitamin D. Formation of this metabolically active form in the kidney is regulated by serum phosphorus and calcium concentrations and parathyroid hormone. The metabolically active form of vitamin D acts to mobilize calcium from bone in order to maintain serum calcium concentration, by maturation and activation of osteoclasts. The precise mechanism by which vitamin D influences bone growth is not completely understood, but may be indirectly through calcium and phosphorus concentration, or through direct interaction with osteoblasts and chondrocytes.⁴

Contributing Institution:

Institute of Veterinary, Animal and Biomedical Sciences, Massey University, Tennant Drive, Palmerston North, New Zealand

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Vol1. Philadelphia, PA: Elsevier Saunders; 2007:1-184.

CASE II: W361-13 (JPC 4052870).

Signalment: Neonatal female donkey foal (*Equus africanus asinus*).



Mandible, donkey: This donkey foal exhibits marked brachygnathism inferior. (Photo courtesy of: Faculty of Veterinary Science, University of Melbourne www.vet.unimelb.edu.au)

History: A middle-aged donkey jenny was presented to the University of Melbourne for imminent parturition. The sire of the foal was unknown. Foaling was routine and the foal was bright and vigorous, but approximately one hour post-parturition the foal suffered a fracture of the right tibia during an attempt to stand. Radiographs indicated a displaced spiral fracture of the distal tibial diaphysis and metaphysis. The tibia and femur also had radiographic evidence of reduced medullary cavity size, thickened mid-diaphyseal cortices, and conical metaphyseal bone extending toward the mid-diaphysis. Due to the suspicion of underlying bone disease, the foal was euthanized with owner consent.

Gross Pathology: The animal displayed marked brachygnathism inferior and failure of dental eruption. All bones were brittle and

easily cut with a knife. There was an acute spiral fracture extending along the left tibia, as well as a non-displaced fracture of the right transverse process of the L2 vertebrae. Focal bone thickenings (callouses) and hemorrhages were present over the midpoint of the ribs bilaterally from T6-T13, and the orientation of the ribs was deviated. On sectioning, all long bones displayed thickened cortices and large cores of intramedullary trabecular bone that extended along the diaphysis from both the proximal and distal metaphysis, with severe reduction in medullary space.

Laboratory Results: None

Histopathologic Description:

Long bone, metaphysis: Extending from the growth plate through the medullary cavity of the metaphysis there is a marked increase in the extent of metaphyseal trabeculae. Trabeculae are disorganized and are composed of irregular cores of retained cartilage derived from the hypertrophic zone of the physis, overlaid and interspersed by mineralized bone. Towards the diaphysis there is a progressive decrease in trabecular size and number, and



Mandible, donkey: Radiographs of the head demonstrate that the teeth are present, but have failed to erupt. (Photo courtesy of: Faculty of Veterinary Science, University of Melbourne www.vet.unimelb.edu.au)

intertrabecular medullary spaces contain foci of hematopoietic cells within loose fibroadipose connective tissue. The cortex is markedly thickened and poorly compacted, with cortical bone arranged in longitudinal lamellae separated by loose fibrovascular and adipose tissue with occasional sparse bone marrow infiltration. Osteoclast numbers throughout the section are markedly decreased, and there is no evidence of reversal lines or Howship's lacunae within the section.



Tibia, donkey: Radiographs of long bones of the hindlimb show a markedly increased density of the diaphysis. (Photo courtesy of: Faculty of Veterinary Science, University of Melbourne www.vet.unimelb.edu.au)

Contributor's Morphologic Diagnosis: Bone: Osteopetrosis, diffuse, donkey (*Equus africanus asinus*).

Contributor's Comment: Osteopetrosis (AKA marble bone disease) is a heterogeneous disease process characterized by defective osteoclastic bone resorption, resulting in failure of bone

remodeling and dense, fragile bones that fracture readily. The condition has been reported in a number of species, including Angus, Hereford and Simmental cattle, Peruvian Paso and Appaloosa horses, white-tailed deer, rabbits and several dog breeds.¹² To the author's knowledge, this is the first case observed in a donkey. Brachygnathia inferior is a common finding in affected animals, reflecting failure of mandibular growth, and dental eruption is typically impaired, as this process requires bone resorption. Anemia has also been reported in some cases, as well as leukopenia and immune deficiencies such as hypoglobulinaemia.^{1,6} Anemic animals often display hepatosplenomegaly due to prominent extramedullary hematopoiesis. Hematological assessment was not performed in the present case, but the presence of abundant hematopoietic tissue within the medullary cavity, as well as a lack of extramedullary hematopoiesis in the liver and spleen, suggest that marrow function was adequate. In humans, failure of bone remodeling has also been associated with nerve entrapment and compression, most commonly manifesting as blindness and



Ribs, donkey: Calluses and hemorrhages, representing previous fractures were seen on ribs 6-13. (Photo courtesy of: Faculty of Veterinary Science, University of Melbourne www.vet.unimelb.edu.au)



Long bones, donkey: Large cores of intramedullary trabecular bone that extended along the diaphysis from both the proximal and distal metaphysis, with severe reduction in medullary space. (Photo courtesy of: Faculty of Veterinary Science, University of Melbourne www.vet.unimelb.edu.au)

deafness, though these feature have not been noted in domestic species.

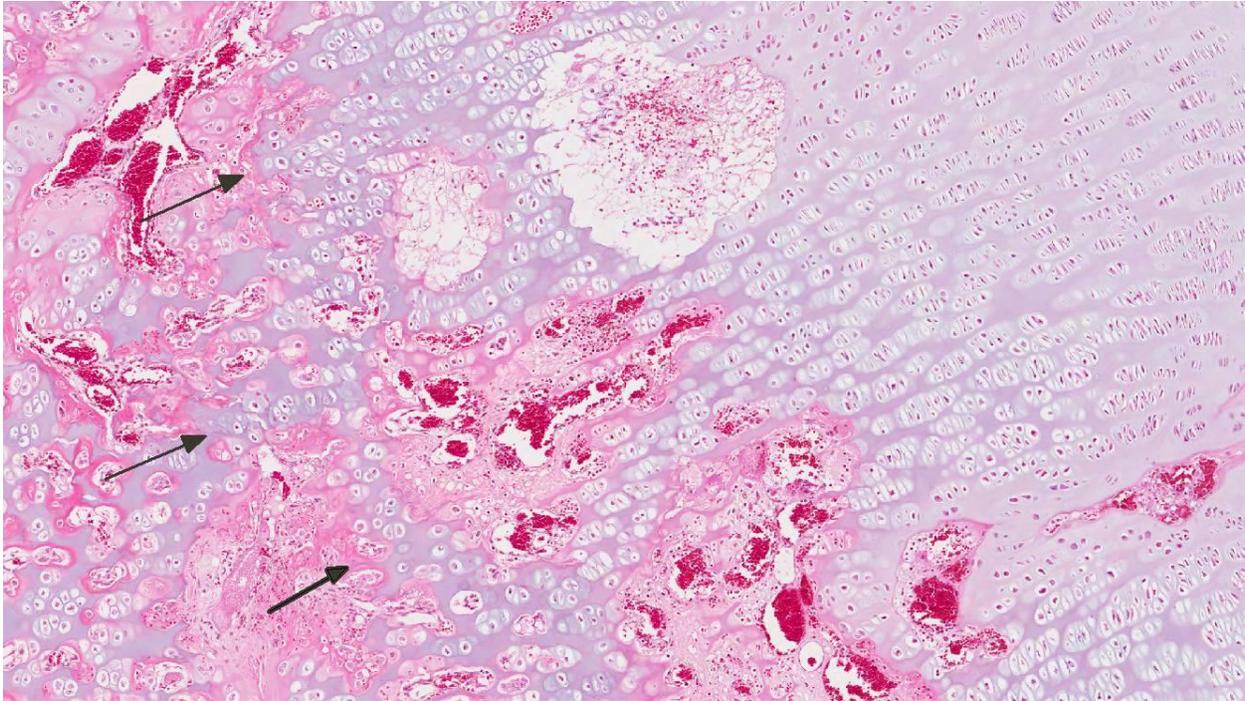
Osteopetrosis occurs in various forms, but the disease typically reflects either functional osteoclast impairment (such as defects in carbonic anhydrase or the H⁺-ATPase proton pump)¹³ or depletion of the osteoclast cell population. Many cases in domestic species are suspected to represent genetic defects with autosomal recessive heritability, but the specific mutation has so far only been identified in Angus cattle, which display a deletion mutation of the *SLC4A2* anion exchanger.⁸ The *SLC4A2* defect results in

failure of acidification at the sites of remodeling and defective bone demineralization. Osteoclasts are rare in the Angus form of disease, but animals with functional osteoclast defects typically have adequate or increased osteoclast numbers, though the osteoclasts may display morphological abnormalities such as hypertrophy, increased numbers of nuclei or absence of a ruffled border.

Osteopetrosis caused by failure of osteoclast development is rare, but osteoclast-poor disease with autosomal recessive heritability exists in humans. Osteoclast differentiation is dependent on RANK/RANKL (Receptor Activator of Nuclear Factor- κ B/ Receptor Activator of Nuclear Factor- κ B Ligand) signaling, and mutations in genes responsible for this receptor/ligand pair (*TNFRSF11A* and *TNFRSF11*, respectively) lead to the profound osteoclast deficiency.^{11,5} In mouse models, osteopetrosis is also observed with defects in a range of other genes associated with osteoclast differentiation, but these



Tibia, donkey. A total lack of physal remodeling has resulted in a thick core of unremodeled primary spongiosa extending into the diaphysis. (HE, 4X)



Tibial physis, donkey. There is marked persistence of the physal zone of hypertrophy. Cartilage cores bridge in a horizontal fashion (arrows) as well as laterally, and there are large areas of degenerate cartilage with minimal osteoid deposition or mineralization. (HE, 35X)

have not been described in natural disease.³ The depletion of osteoclasts in the present case suggests it may be a different form of osteopetrosis to that described in most other equine cases, which typically display normal to increased osteoclast numbers. However, a single case of osteoclast-poor osteopetrosis has been reported in a Peruvian Paso foal.⁸

Acquired osteopetrosis-like disease has been reported secondary to a number of viral infections, presumably reflecting viral osteoclast tropism and cell depletion. Zonal lesions consistent with osteopetrosis have been reported with bovine viral diarrhoea virus in cattle,⁹ and similar features have been identified in the metaphyseal region of dogs with distemper and cats infected with feline leukaemia virus.¹² Osteosclerotic disease similar to osteopetrosis has also been reported associated with

hypervitaminosis,⁶ lead poisoning,¹² and exogenous oestrogen⁵ and glucocorticoid administration.⁴ Cases of rickets may display retention of cartilaginous metaphyseal trabeculae overlaid by osteoid, similar to those observed in osteopetrosis. In rickets, however, the trabeculae are poorly mineralized, while the bone in cases of osteopetrosis undergoes normal mineralization.

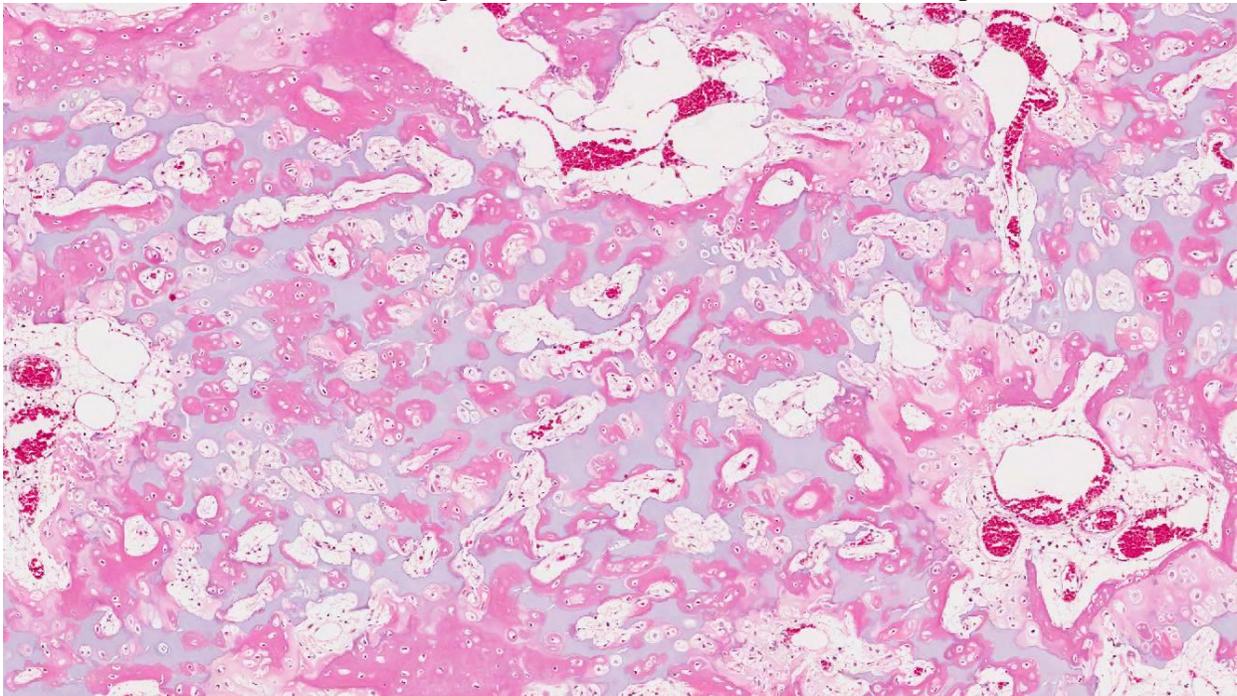
JPC Diagnosis: Long bone: Physal dysplasia, diffuse, severe with osteoclast depletion, failure of chondroclasis, cortical osteopenia and diffuse medullary osteosclerosis (osteopetrosis).

Conference Comment: The histologic description discussed in conference was very similar to the contributor's. The noted primary features included increased bony trabeculae arranged in disorganized transverse and longitudinal arrays with

persistent cartilage cores, absence of osteoclasts, decreased bone marrow elements, absence of a cutback zone and cortical osteopenia. The physal zones involved in endochondral ossification appear histologically normal until subjacent to the zone of hypertrophy, where osteoclasts would normally be present remodeling mineralized cartilage, but in this case are absent. Cortical osteopenia, including multiple thin, widely separated longitudinal bands of bone, was also described and discussed as a feature not commonly associated with osteopetrosis, and there was speculation it may reflect a secondary process. The gross images were viewed during conference, and there was discussion regarding the multiple callouses and hemorrhages on the ribs being secondary to in utero fracture.

There are two main forms of osteopetrosis described in humans: a recessively inherited lethal form in which lesions are present at

birth, and a dominant form which manifests in adults.² Osteopetrosis in Red Angus calves with a deletion mutation in the gene *SLC4A2*, which encodes the anion exchanger for carbonate and chloride, has recently been compared to the recessive form which occurs in children, and aspects of the craniofacial lesions were found to be similar. Craniofacial lesions in affected calves include dorsoventrally compressed brains with depressions of the parietal cortex due to thickening of the parietal bone; compression of the cerebral hemispheres with vermis herniation through the foramen magnum; chromatolysis in multiple cranial nerve nuclei; optic nerve atrophy; loss of retinal ganglion cells; and dysplastic changes in the molar and premolar teeth. There was also corpora amylacea in the thalamus, basal nuclei and midbrain, and mineralization in vessels of the thalamus. One important difference noted between the condition in Red Angus calves and the recessive lethal form in humans is the presence of increased



Tibial diaphysis, donkey. There is extensive unremodeled and degenerating primary spongiosa with thin lining osteoid seams within the diaphysis. Marrow spaces are markedly decreased in volume and lack hematopoietic precursors. (HE, 35X)

numbers of osteoclasts in people, while decreased numbers of osteoclasts were present in the long bones of affected calves. Osteoclast numbers in calves, however, were more normal in bones of the head. Affected calves died in utero or shortly after birth and were either homozygous or heterozygous for the *SLC4A2* mutation, respectively.⁹ Long bone lesions in affected calves included dense unresorbed bony trabeculae from the metaphysis to the central diaphysis, similar to what is present in other species.²

The specific type of osteoclast defect present influences the number of osteoclasts, whether increased, decreased, or absent, in various types of osteopetrosis. For example, in mutations involving the chloride channel (*CICN7*) or the proton pump (*ATP6i*), osteoclasts may be present in increased numbers but are nonfunctional; however, in mutations involving the *RANKL* gene, necessary for proper osteoclast differentiation, osteoclasts are decreased or absent. Osteopetrosis in Hereford and Simmental breeds of cattle is similar to the condition in Angus calves. One difference is the presence of thickened frontal bones with cystic spaces, creating a domed forehead that can be mistaken for hydrocephalus. Osteopetrosis is described in Belgian Blue cattle in Europe in combination with abnormal skull formation and mandibular gingival hamartomas. A mutation was identified in the chloride / proton exchanger lysosomal anion transporter *CICN7* in affected calves. Osteopetrosis is also described in inbred Polypay sheep and white-tailed deer, both of which also have brachygnathia inferior, a common finding in many affected species. The white-tailed deer also have calluses on several ribs, similar to the disease in horses, suggesting in utero rib fractures. Osteopetrosis has been documented in dogs but is poorly characterized.²

Contributing Institution:

Faculty of Veterinary Science, University of Melbourne

www.vet.unimelb.edu.au

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CASE III: 13073102 (JPC 4053418).

Signalment: 24 week-old male Lewis rat (*Rattus norvegicus*)

History: The L5 lumbar intervertebral disc was subjected to surgical puncture. Necropsy and tissue collection were performed two months post-procedure.

Gross Pathology: No description provided

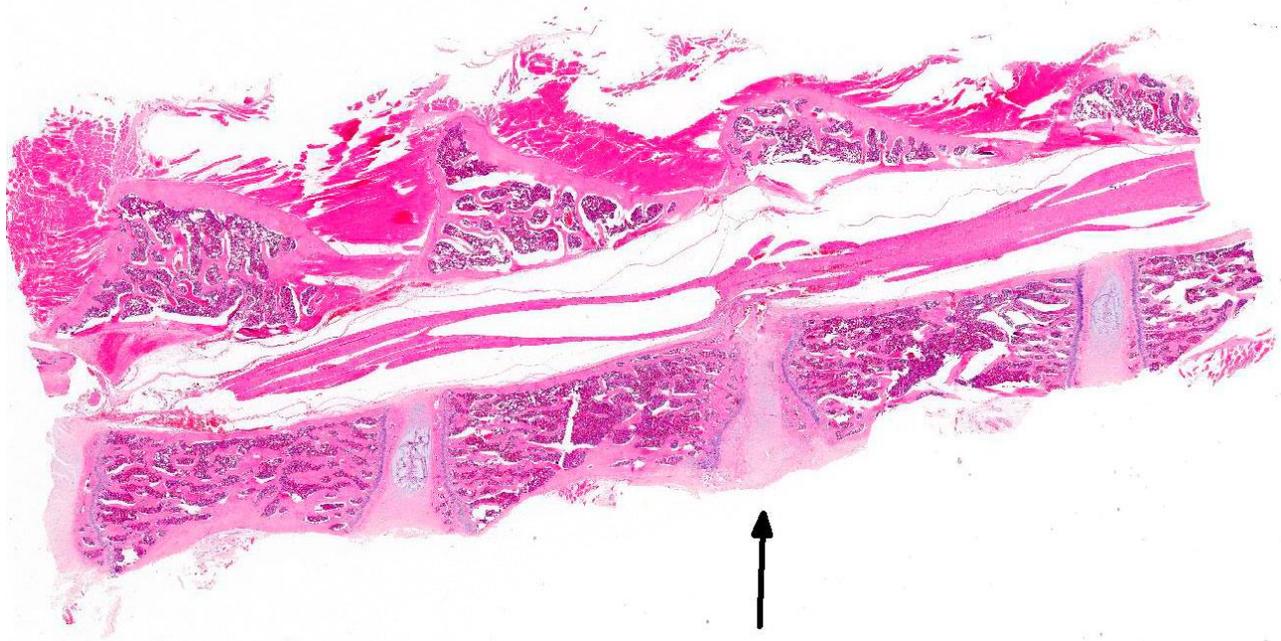
Laboratory Results: N/A

Histopathologic Description: Located centrally within this parasagittal section of decalcified lumbar spinal column is a degenerate intervertebral disc flanked by two normal discs. The degenerate disc exhibits loss of the central nucleus pulposus and

replacement of the normal lamellar arrangement of the annular fibrosus by disorganized fibrocartilage and hyaline cartilage (Figure 1). In particular, the dorsal annulus has been replaced by a mass of disorganized hyaline cartilage capped by proliferating fibrovascular tissue and metaplastic woven bone that bulges into the spinal canal and compresses overlying degenerating cauda equine nerves. On one side of the degenerate disc, epiphyseal lamellar bone and portions of physeal cartilage have been replaced by disorganized hyaline cartilage containing zones of granular degenerate matrix (Figure 2). Residual physeal cartilage is variably disorganized and there is mildly increased thickness of adjacent metaphyseal trabecular bone (osteosclerosis).

Contributor's Morphologic Diagnosis: Intervertebral disc: Degeneration, focal, chronic, with focal osseous metaplasia and compressive cauda equina nerve degeneration.

Contributor's Comment: Vertebral disc degeneration is a serious condition in humans that may occur during aging or be induced through injury. Vertebral disc degeneration results in a diminished load carrying capacity leading to the inability to perform basic tasks.³ Several animal models have been developed to mimic human vertebral disc degeneration (Table 1), often involving mechanical interventions such as altered loading, altered motion, or incited disc injury, and are used to explore disease pathogenesis and to test possible treatments. Important considerations for the selection of the model system and interpretation of experimental results are related to differences in anatomy, physiology, and biomechanics between humans and the various model species.¹ The



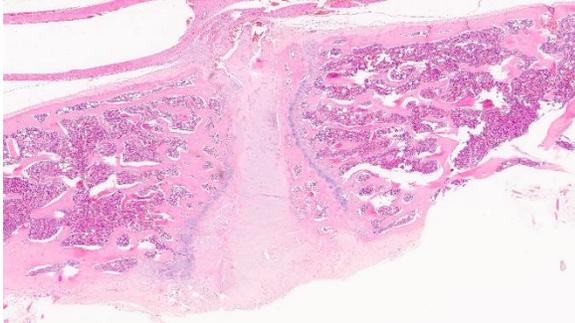
Thoracic spine, rat. One vertebral space is compressed (arrow) due to removal of the nucleus pulposus. (HE, 5X).

case presented here involves a rat model of vertebral disc degeneration in which a minor needle puncture injury to the annulus fibrosus causes degenerative changes in the intervertebral disc and adjacent vertebrae.

The normal intervertebral disc is avascular and primarily aneural. It is comprised of a dynamic extracellular matrix as well as a fibrocartilaginous network that maintains tensile strength. Importantly, there is normally a clear morphological distinction between the peripheral annulus fibrosus (AF) and inner nucleus pulposus (NP).⁹ The composition of the outer AF is primarily type I collagen fibers that are aligned at approximately 30° angles to the longitudinal axis of the spine. The direction of the type I fibers alternates in each concentric layer of the disc in an orientation designed to provide maximal strength. These collagen fibers also align with the cells of the AF, which are fibroblast-like with elongated nuclei. The inner layer of the disc, the nucleus pulposus

(NP), contains a viscous proteoglycan gel, a small amount of type II collagen, and (in humans; see more below) chondrocyte-like, rounded cells.⁵ The proteoglycan gel is primarily composed of aggrecan, which is extremely hydrophilic. The aggrecan absorbs water and creates a swelling pressure responsible for maintaining tissue hydration and balancing the osmolarity of the disc.⁹ Consequently, a hydrostatic pressure is created within the nucleus, which is contained by the lamellae of the annulus, and distributes loads evenly across the underlying/adjacent vertebrae.³

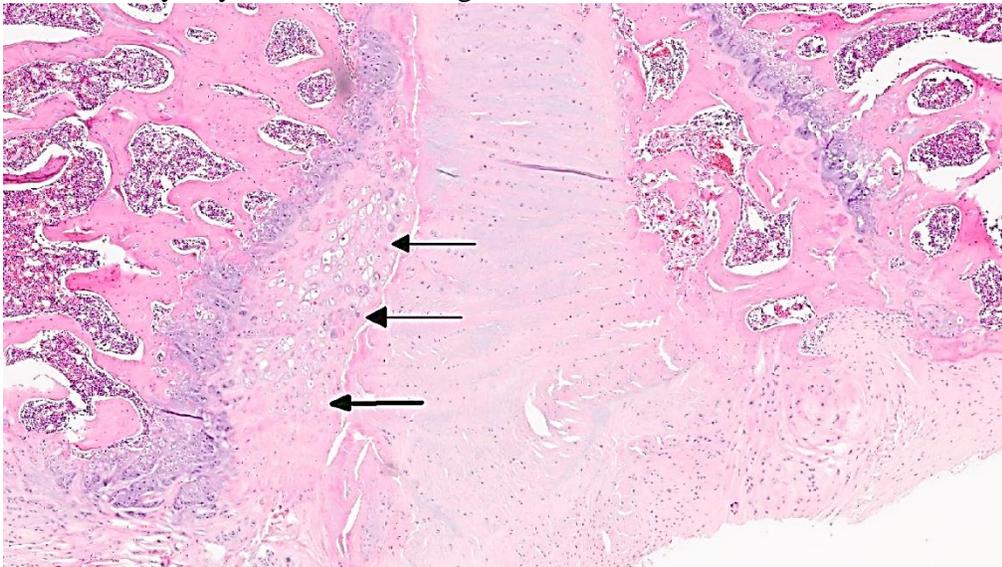
Vertebral disc injury causes a degradative cascade that leads to both physiological and morphological changes. The degenerative changes involve increased breakdown of matrix, altered matrix synthesis, and cell loss through apoptosis. Fissures in the outer annulus may cause bulging of the disc⁴ and aggrecan degeneration of the nucleus pulposus leads to infiltration of nerve endings and blood vessels into the normally avascular



Higher magnification of the anuclear disk space. (HE, 8X)

disc, resulting in pain. Loss of aggrecan also causes a decrease in hydration and swelling pressure, causing decreases in disc height and alterations in load carrying capacity.⁹

In a damaged disc, there eventually is no clear morphologic distinction between the AF and the NP. Over time, the organization of the chondrocyte-like NP cells is lost as these cells are replaced by fibrosis characterized by decreased type II collagen and increased type I and type X collagen.^{4,5} The predictable pattern of the AF cells becomes disorganized as cells are lost or become arranged in clusters.⁹ Finally, disc injury also causes the recruitment of inflammatory cytokines and degradative

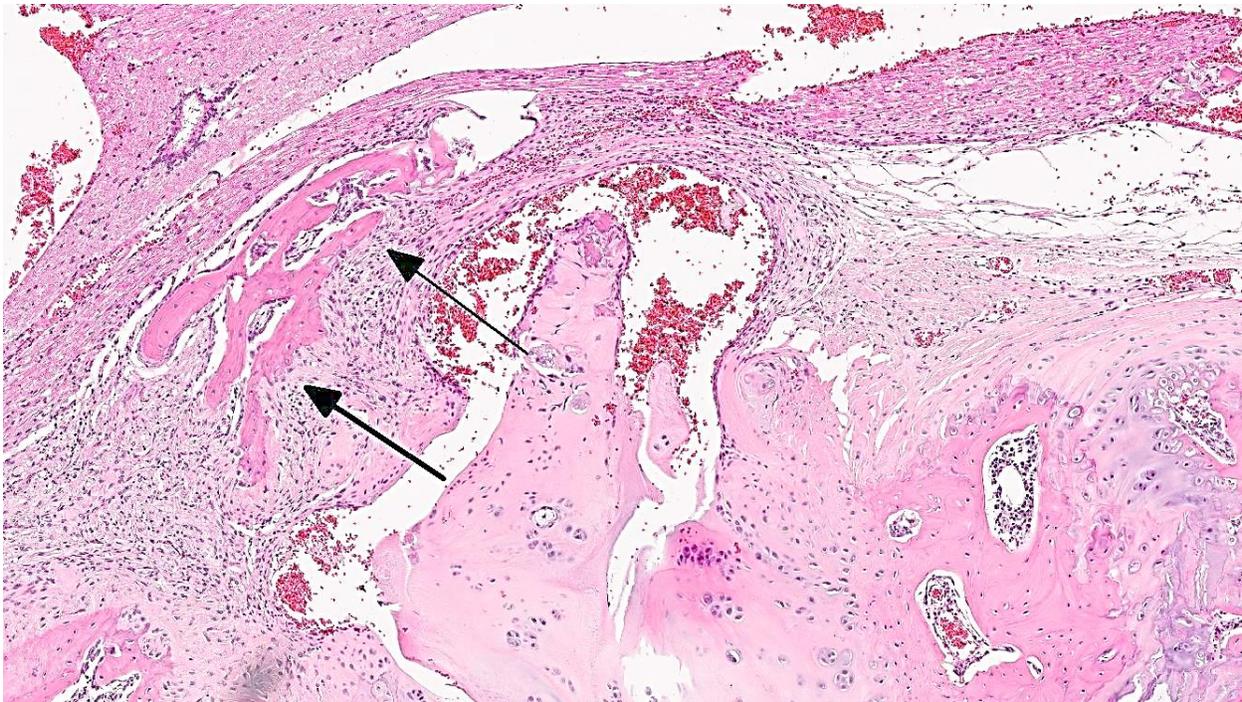


There is remodeling and thickening of the vertebral endplate to the compressed disk space. The remodeled endplate contains disordered chondrones of proliferating chondrocytes. (HE, 39X)

enzymes. IL-1, the primary cytokine in the damaged disc, inhibits the production of the extracellular matrix and stimulates additional cytokine production.⁵ As additional cytokines are recruited to the damaged disc, apoptotic cell death ensues.

There are several differences in the development, cell composition, anatomy, physiology, and mechanical properties of intervertebral discs between humans and animals.¹ The composition of the nucleus pulposus and the organization of the cartilage endplates are two notable examples of differences between humans and many animal species. Throughout the life of rats the nucleus pulposus is composed of notochordal cells, which are large, highly vacuolated, loosely arranged, produce large quantities of hyaluronin, and influence the metabolism of other cell types within the disc. In contrast, numbers of notochordal cells decrease rapidly in the nucleus pulposus of young humans and in adults are replaced by chondrocytic cells.

In rats and many other species the secondary ossification centers of the vertebral body form a complete osseous epiphyseal plate between the intervertebral disc and the vertebral body physis and this persists throughout the life of the animal. In humans, however, the epiphysis from the secondary ossification center exists as a ring adjacent to the outer



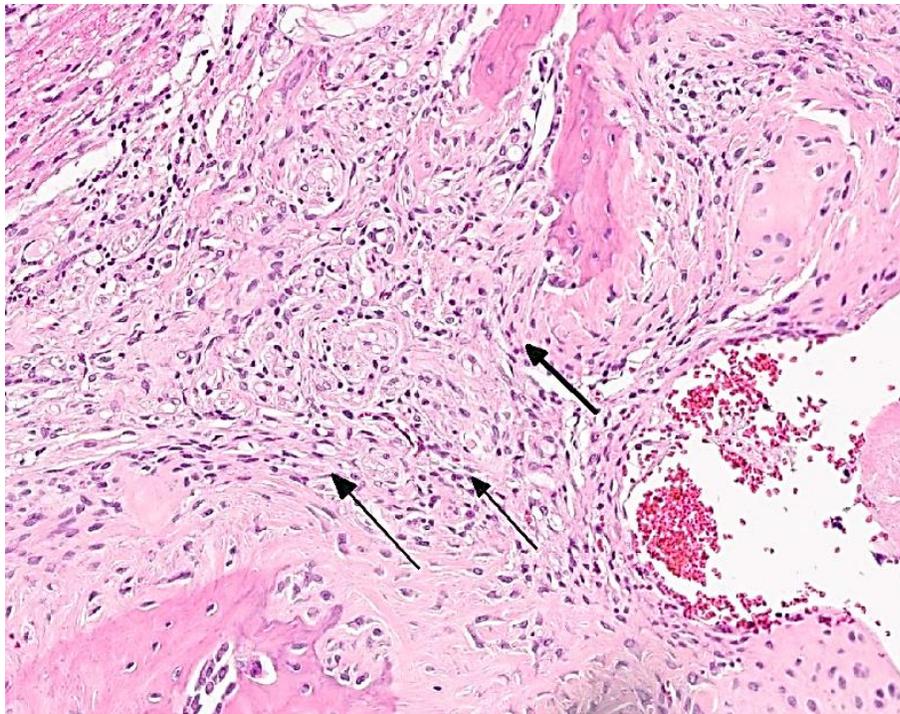
The degenerating annulus fibrosus (surrounded by a venous sinus) is prolapsed dorsally against the ventral longitudinal ligament. There is an osteophyte of woven bone embedded within a focus of fibrosis involving spinal nerves and the ventral longitudinal ligament adjacent to the prolapsed disk (HE, 50X).

annulus fibrosus rather than as a complete plate adjacent to the disc and the physis closes at about 25 years of age. Because of this the base of the cartilage endplate acts as the growth region for the vertebral body in humans while in most other species vertebral body growth occurs via the epiphyseal plates. The relevance and translatability to humans of results obtained from studies of disc degeneration using animal models must consider the potential impact of differences such as these.

JPC Diagnosis: Intervertebral disc: Disc rupture and prolapse with degeneration of the annulus fibrosus, end plate collapse, vertebral osteophytosis and mild focal spinal nerve compression and degeneration.

Conference Comment: The contributor provides a thorough histologic description which is very similar to the description given during the conference. There was

speculation as to whether the small section of bone dorsal to the vertebral body represents an osteophyte or is bone fractured during the surgical puncture procedure. Additionally, a focal area with interwoven streams and bundles of spindle cells adjacent to this area of bone has a distinct neural morphology, and there was conjecture whether this may represent an incipient traumatic neuroma. The chondrocytes were described as being hypertrophied, hyperplastic and reactive, manifesting as multiple large chondrocytes trapped within a single lacuna. There were also areas of chondrocyte necrosis and the vacuolated, degenerate chondrocytes. The moderator led a discussion on how bone reacts to injury, demonstrated in this case as epiphyseal endplate merger with the annulus fibrosus, a manifestation of degenerative intervertebral disc disease. Please note, the digital image is upside down and must be flipped vertically for the proper anatomic orientation.



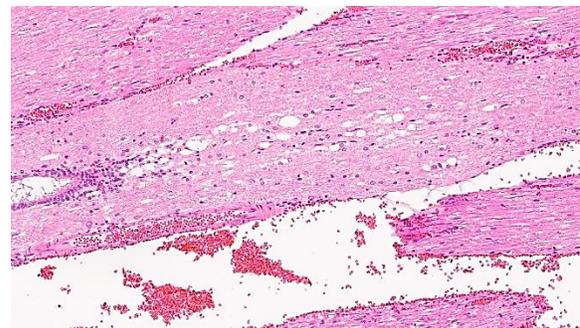
There is a focal proliferation of small nerve bundles (neuroma) immediately adjacent to the dorsal aspect of the prolapsed disk. (HE, 65X)

Degeneration of intervertebral discs is a particularly important disease not only in people, but also in dogs. It occurs in all dog breeds but there are significant differences in the pathogenesis between chondrodystrophic and nonchondrodystrophic breeds. Chondrodystrophic breeds have an increased expression of fibroblast growth factor 4 (FGF4), which affects not only appendicular skeleton formation, but also the composition of the nucleus pulposus (NP) in their intervertebral discs. In these breeds the NP contains a much greater content of collagen than proteoglycan, and collagen content can increase over time in the degeneration process, decreasing water content and the disc's ability to adequately absorb mechanical forces. The NP begins to degenerate very early in life, and microscopically this is seen as chondrocyte proliferation and lobulation of the NP. These changes occur in all intervertebral discs. Eventually the NP with higher collagen content begins to degenerate, harden and may

mineralize, becoming friable, and the inner aspects of the annulus fibrosis (AF) can also begin to degenerate and tear, allowing fragments of NP to enter the AF. These changes can extend through the AF, resulting in a Hansen type I intervertebral disc herniation, with fragments of degenerate NP extending through the dorsal longitudinal ligament into the spinal canal. This most frequently results in local myelomalacia in the affected spinal cord region with

accompanying inflammation, but can result in ascending myelomalacia in some severe cases.²

Nonchondrodystrophic breeds do not suffer the same type of degeneration and mineralization of the NP as chondrodystrophic breeds. The NP in their intervertebral discs may undergo degeneration and fibrous metaplasia, but it occurs later in life and generally only affects a single disc or few discs are involved, and



Dorsal to the prolapsed annulus fibrosis, the spinal cord contains low to moderate numbers of dilated myelin sheaths. (HE, 75X)

the degeneration is thought to be related to trauma and disruption of the annulus fibrosis. These changes result in a Hansen type II herniation which refers to partial herniation of the NP through the AF, bulging of the AF, and compression of the dorsal longitudinal ligament, which may then impinge on the spinal cord. Type II herniations in general result in less severe disease. Disc herniations most commonly occur dorsally or dorso-laterally, but can also occur ventrally, cranially and caudally. Cranial and caudal herniation of the nucleus pulposus into the vertebral body creates a lesion known as a Schmorl's node within the vertebral endplate. Intervertebral disc herniations are rare in other species but have been documented in the cervical region of horses, similar to type II lesions in dogs. Sows and boars have also been documented to have degenerative intervertebral disc changes, but not dorsal herniation of the NP.²

Contributing Institution:

Eli Lilly and Company, Investigational Pathology, Indianapolis, IN 46285
www.lilly.com

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CASE IV: 66898 (JPC 4066452).

Signalment: 7-year-old, female intact, reticulated giraffe (*Giraffa camelopardalis reticulata*).

History: This adult female reticulated giraffe was born and housed at the Maryland Zoo in Baltimore. In 2011, the animal had an acute onset of right front limb lameness with swelling of the right front fetlock. Traumatic injury was suspected. Although the animal improved slightly with multiple courses of treatment (topical and systemic non-steroidal anti-inflammatory medications, chondroprotective supplements, analgesics and topical steroids), lameness and swelling in the right front fetlock persisted with episodes of acute



Carpal joint, giraffe. Upon opening, the carpometacarpal joint has extensive proliferation of hemorrhagic tissue within the joint, as well as marked thickening of the joint capsule. (Photo courtesy of: Department of Molecular and Comparative Pathobiology, Johns Hopkins University, 733 N. Broadway, Suite 811, Baltimore, MD 21205)

worsening of clinical signs over a 3-year period. Ultrasonography and thermography of the fetlock in early 2012 showed changes consistent with chronic osteoarthritis. Intra-articular injections of hylartin and depomedrol were performed with minimal improvement. Ultimately, the animal was euthanized in 2014 at the age of 17 due to progression of chronic lameness.

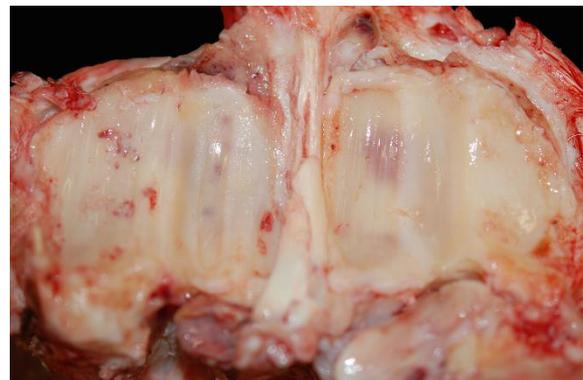
Gross Pathology: At necropsy, the right front fetlock was severely swollen and soft on palpation. Aspiration of the affected joint yielded a large amount of turbid red fluid with low viscosity. Joint fluid cytology revealed many non-degenerate neutrophils, with occasional lymphocytes and macrophages on a proteinaceous background. Aerobic bacterial culture of joint fluid was negative. The articular surface of the carpometacarpal joint contained multiple variably-sized areas of cartilage fibrillation and erosion, and in several areas there was exposure and eburnation of the underlying subchondral bone. The periarticular cartilage contained numerous small osteophytes. The synovial lining was diffusely thickened and discolored red to tan, with numerous small pinpoint areas of hemorrhage. On the palmar aspect of the fetlock, deep to the deep digital

flexor tendon, the tendon sheath was multifocally adhered to the underlying fascia by abundant, dark red-brown granulation tissue. Within this reactive tissue and also multifocally throughout the joint capsule were multiple variably sized firm yellow-tan smooth nodules, which were well demarcated and encapsulated.

Additional gross findings in this animal included mild to moderate, chronic active osteoarthritis in multiple joints with varying degrees of fibrinous effusion and synovial hyperplasia, multifocal renal cortical fibrosis, severe dental disease, and a benign ovarian tumor.

Laboratory Results: None

Histopathologic Description: Submitted slides may contain sections of synovium and tendon sheath or just tendon sheath. Arising from the flexor tendon sheath is a well-demarcated, partially encapsulated, densely cellular mass. The majority of cells within the mass resemble well-differentiated macrophages and fibroblasts on an intervening dense collagenous stroma. A low number of cells (less than 10% of the cell



Carpal joint, giraffe. The articular surface of the carpometacarpal joint contained extensive cartilaginous fibrillation and erosion, with multifocal exposure and eburnation of the underlying subchondral bone. (Photo courtesy of: Department of Molecular and Comparative Pathobiology, Johns Hopkins University, 733 N. Broadway, Suite 811, Baltimore, MD 21205.)

mass) are characterized by abundant eosinophilic finely vacuolated cytoplasm, large size (up to 200um), and contain up to 50 nuclei arranged centrally within the cell. There is mild multifocal hemorrhage throughout the mass, and macrophages frequently contain abundant brown granular pigment, which stains positively with Prussian blue (hemosiderin). The mass is diffusely infiltrated by moderate numbers of neutrophils along with fewer lymphocytes and plasma cells, and is almost entirely surrounded by a dense fibrous connective tissue capsule.



Joint capsule, giraffe: The synovium of the affected joint is thrown into thick frond-like villar projections. (HE, 5X)

The synovium of the affected fetlock is diffusely and markedly hyperplastic with numerous thick frond-like villous projections. The synovium is expanded by a large population of mixed inflammatory cells with large numbers of neutrophils, and moderate granulation tissue. Occasionally, hyperplastic synovial villi contain large multinucleated cells, which are morphologically identical to those seen within the nodule in the adjacent tendon sheath.

Immunohistochemically, large multinucleated cells all exhibit strong, cytoplasmic reactivity for cathepsin K and moderate cell membrane reactivity for IBA-1 (ionized

calcium-binding adapter molecule 1). Multinucleated cells were negative for lysozyme immunostaining. Mononuclear, macrophage-like cells throughout the mass exhibit strong cytoplasmic reactivity for cathepsin K, while a smaller proportion of mononuclear cells showed moderate cytoplasmic reactivity for IBA-1 and lysozyme.

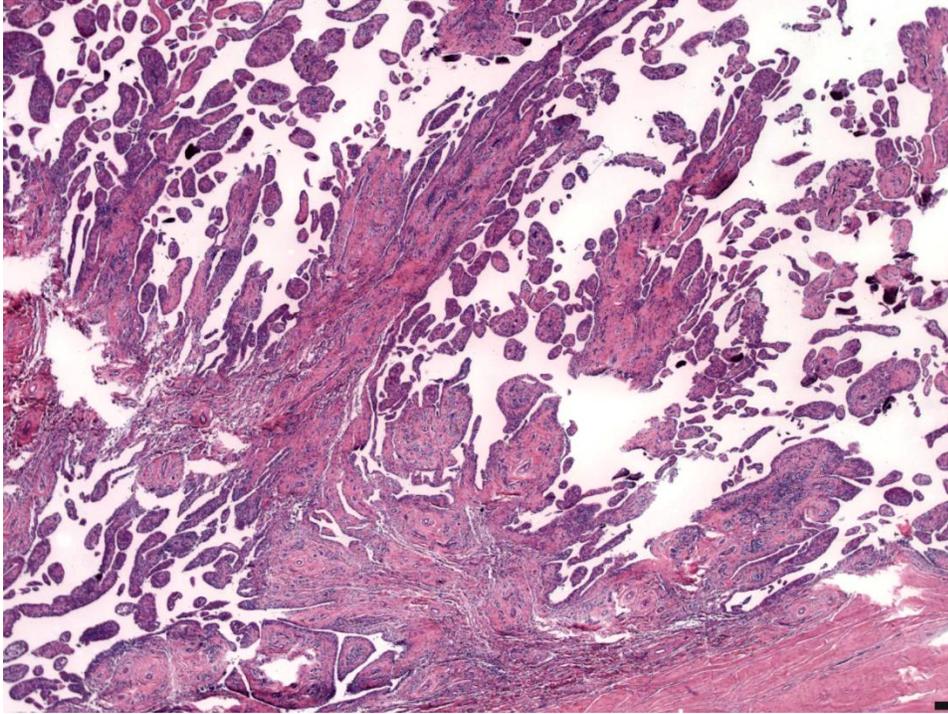
Contributor's Morphologic Diagnosis:

Fetlock, pigmented villonodular tenosynovitis, diffuse, chronic-active, severe with moderate neutrophilic inflammation, hemorrhage, and moderate intrahistiocytic hemosiderin.

Contributor's Comment:

Gross and histologic findings in this case are consistent with a diagnosis of pigmented villonodular tenosynovitis (PVNS), a condition which occurs in humans and has been reported in a range of animal species including dogs, horses, and a European lynx.^{3, 5, 7} Nodules seen in this condition are characterized histologically by abundant connective tissue, heavy macrophage and fibroblast infiltration, and large multinucleated giant cells which morphologically resemble osteoclasts. The pigmented appearance of these nodules is the result of intrahistiocytic hemosiderin accumulation thought to be secondary to recurrent intra-articular hemorrhage. This syndrome belongs to a group of histologically similar conditions that likely represent a spectrum of the same process. Localized forms are also sometimes referred to as "localized nodular tenosynovitis" or "benign giant cell tumor of tendon sheath."

The etiology of this condition is uncertain, with debate over whether these lesions represent a primarily neoplastic or inflammatory process. Although these lesions are considered almost universally benign, rare reports of distant metastasis have occurred,¹ and localized forms may exhibit local recurrence after surgical excision.⁸



Joint capsule, giraffe. Higher magnification of the villar synovial proliferation. (HE,40X) (Photo courtesy of: Department of Molecular and Comparative Pathobiology, Johns Hopkins University, 733 N. Broadway, Suite 811, Baltimore, MD 21205.)

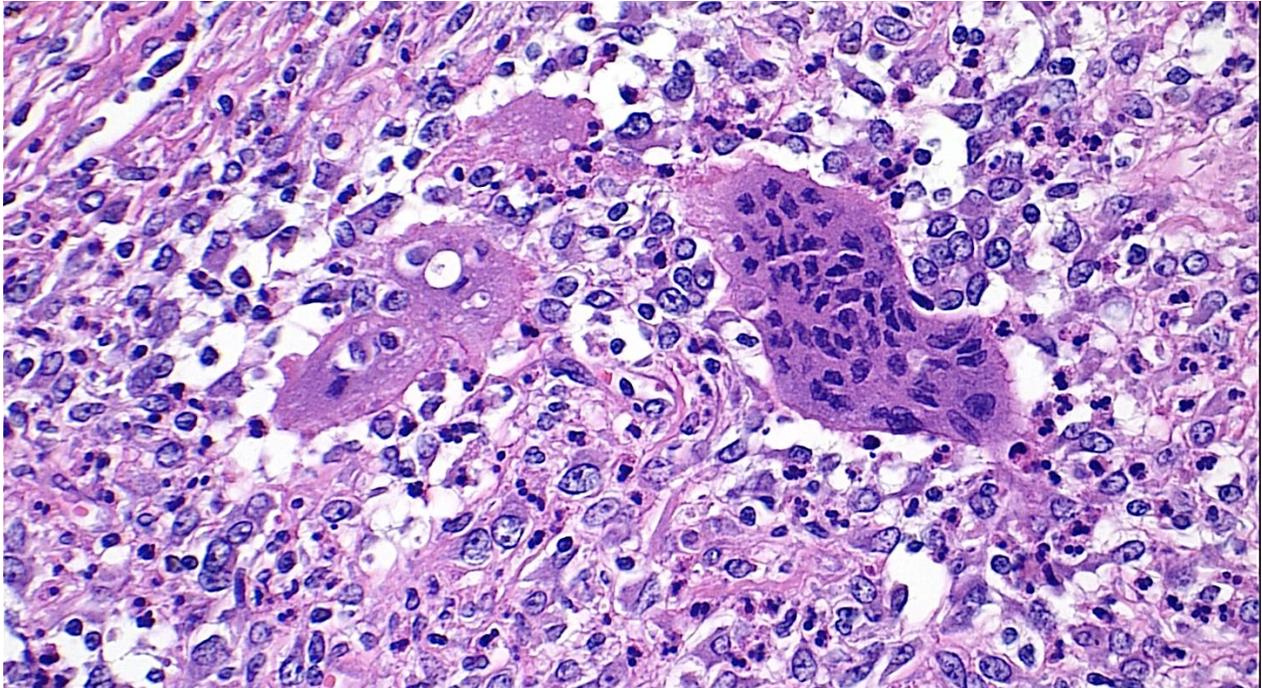
Genetic analysis of human cases of PVNS has revealed a cluster of non-random clonal chromosomal translocations, with multiple cases sharing similar breakpoints on several chromosomes.⁶ Interestingly, a majority of lesions share a break in the region of chromosome 1 which encodes macrophage colony stimulating factor (CSF1), a cytokine important for macrophage differentiation and proliferation. CSF1 is known to play an important role in the pathogenesis of numerous inflammatory arthritides, including rheumatoid arthritis. Recent theories on PVNS suggest a “landscaping effect” as part of the pathogenesis, with a low number of neoplastic cells overexpressing CSF1, resulting in recruitment of large numbers of mononuclear inflammatory cells which make up the bulk of the lesion.^{4,9}

In humans, 40-75% of PVNS cases have a history of previous trauma to the affected joint.⁵ Similar to this giraffe, lesions in people occur most frequently in high-use

joints of the distal limbs, and are more frequently associated with the flexor surface. In this giraffe, no evidence of trauma was found grossly or radiographically at necropsy. However, based on the extended history, an episode of previous acute trauma or repetitive microtrauma cannot be excluded. Cultures of the synovial fluid from the affected joint were negative, and special stains of microscopic

specimens were all negative for infectious organisms, making an infectious etiology unlikely.

The histogenesis of the large multinucleated cells remains elusive. Several cell types of origin have been proposed, including synovial mesenchyme, synoviocytes, tissue macrophages, and cells of osteoclastic lineage. In the case of this animal, IHC yielded inconclusive results as to the origin of these unusual cells, with multinucleated cells expressing IBA1 (a cytoplasmic marker of macrophages) predominantly along the cell membrane, and showing diffuse strong cytoplasmic positivity for cathepsin K (a cysteine protease responsible for matrix-degradation). While cathepsin K has traditionally been used as an osteoclast marker, recent reports have shown expression is not limited to osteoclasts. Cathepsin K expression has also been demonstrated in conditions resulting in high macrophage



Joint capsule, giraffe. The synovium is expanded by a mixed inflammatory population of numerous polygonal and spindle histiocytes, fewer neutrophils, and low numbers of multinucleated giant cells. (Photo courtesy of: Department of Molecular and Comparative Pathobiology, Johns Hopkins University, 733 N. Broadway, Suite 811, Baltimore, MD 21205.) (HE, 400X)

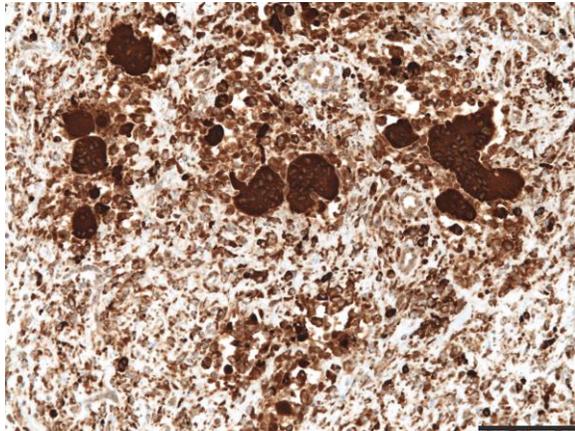
activation, such as granulomatous diseases (tuberculosis and foreign-body granulomas), sarcoidosis and sarcoid-like lesions, and is expressed by both macrophages and multinucleated giant cells in these conditions.² In the case of this giraffe, high expression of cathepsin K by cells in the tendon sheath and synovium may have contributed to osteoarthritic changes.

Inflammation and degenerative changes were also seen in other joints – namely, the contralateral fetlock, both hocks, and the right stifle. Lesions were characterized by a range of changes, from multifocal cartilage fibrillation and erosion to focal chondromalacia, effusive synovitis/bursitis with fibrin and synovial villous hyperplasia. These lesions likely represent the effects of chronic forelimb lameness resulting in altered weight bearing in the other limbs as a compensatory response.

JPC Diagnosis: Synovium and adjacent tendon: Synovitis and tenosynovitis, neutrophilic and histiocytic, villous and nodular, diffuse, severe with multinucleate giant cells and hemosiderophages.

Conference Comment: Conference participants agreed this was a very interesting and challenging case, and there was significant slide variation which increased the level of difficulty. One subset of slides contains only a section of the nodular tissue, making tissue identification enigmatic. Three important aspects of the description in this case included tissue identification based on the presence of tendon on the slide, the villous proliferation of synovium, and the formation of “pigmented” nodules containing fibrovascular tissue and inflammatory cells encased in a dense fibrous capsule. Only a small subset of slides contains all three fea-

tures and many slides contain only the pigmented nodule surrounded by fibrous tissue. The section containing all features is scanned online and it is recommended conference contributors view the virtual slide online to gain a better appreciation of the villous synovial proliferation and tendon changes.

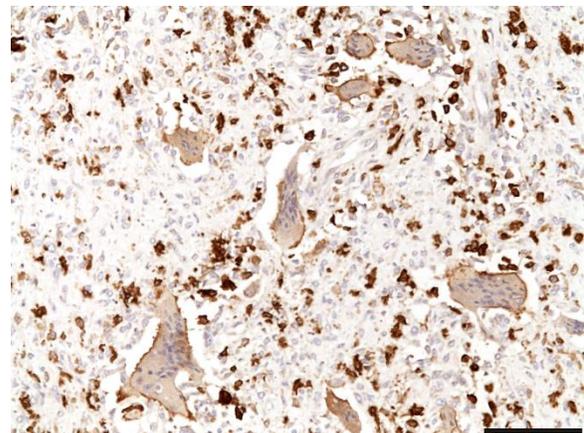


Joint capsule, giraffe. Macrophages and multinucleated giant exhibit strong cytoplasmic positivity for cathepsin K. (Photo courtesy of: Department of Molecular and Comparative Pathobiology, Johns Hopkins University, 733 N. Broadway, Suite 811, Baltimore, MD 21205.)

Conference participants described the nodular mass as fibrovascular tissue containing numerous inflammatory cells including neutrophils, macrophages, many with hemosiderin, and multinucleate giant cells with fewer lymphocytes and plasma cells. The nodule also has multifocal areas containing fibrin, hemorrhage and edema. Fibroblasts or fibroblast-like cells are hypertrophic and multifocally hyperplastic, and the collagenous stroma is haphazardly arranged and appears fibrillated in many areas; some participants described the histologic features of the nodular mass as pseudoneoplastic. Within sections of tendon histologic findings include degeneration and loss of nuclei, areas of hypercellularity, fraying of fibers, and side-to-side fusion and necrosis, all indicative of degeneration. The synovium is observed as proliferative and inflamed; the conference moderator

discussed that because the synovium lines both tendons and joint spaces, that a reactive and inflamed synovium can result in the formation of adhesions. Conference participants speculated as to whether the villous proliferation of synovium originated from synovium lining a tendon, or from the synovium lining the joint space; ultimately participants concluded it was difficult to determine with certainty in this case.

This interesting case also was studied in consultation with the Department of Soft Tissue Pathology at the Joint Pathology Center, whose medical pathologists are familiar with tenosynovial giant cell tumor as described in humans. The medical pathologists agreed the histomorphologic features from the lesion in this giraffe resemble those of tenosynovial giant cell tumor as it occurs in humans; they also observed sheets of plump polygonal cells admixed with osteoclast type giant cells in a collagenized stroma. The medical pathologists also observed a neutrophilic and plasma cell infiltrate in the lesion, and commented that this is not a typical finding of tenosynovial giant cell tumor in people. They speculated that in the case of this



Joint capsule, giraffe: Macrophages show cytoplasmic reactivity and MNGCs show membrane reactivity to IBA-1. (Photo courtesy of: Department of Molecular and Comparative Pathobiology, Johns Hopkins University, 733 N. Broadway, Suite 811, Baltimore, MD 21205.)

giraffe, the inflammatory component may be indicative of an unrecognized infection, an autoimmune component, or possibly inflammatory recruitment by the tumor cells.

This is an interesting case in that the nature, origin and cause of the nodular lesion is unclear. As described above, there is indeed uncertainty in the literature regarding whether this is a neoplastic or inflammatory lesion. As seen in this case and described in others, the nodular proliferation is histologically distinct and different from the adjacent reactive hyperplastic villous synovium. When described as a neoplasm, many different patterns have been described in the literature, with the common thread being the presence of multinucleated giant cells.⁷ The nodules have been described as proliferations of synovial cells, admixed with inflammatory cells including multinucleate giant cells,³ with the cell of origin described as synoviocytes without anaplastic features⁷ or synovioblastic mesenchyme.⁵ In other reports, the giant cells have been described as a proliferation of neoplastic epithelioid to pleomorphic mononuclear cells admixed with fibroblast like cells.⁵ In this giraffe it is unclear if the nodules viewed histologically originated from the tendon sheath, the joint capsule, or from both locations; at necropsy, nodules were described grossly by the contributor as associated with both the tendon sheath and the joint capsule. Exact anatomic origin or location within or adjacent to the joint may not be critical, as it is recognized that there is an overlap in the appearance of lesions whether described as giant cell tumor of tendon sheath, localized nodular tenosynovitis, or pigmented villonodular synovitis of joints.⁷

Contributing Institution:

Department of Molecular and Comparative Pathobiology
Johns Hopkins University

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