The Armed Forces Institute of Pathology
Department of Veterinary Pathology
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1925 Coffey Road
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CASE I – 02-1657 (AFIP 2888700)

Signalment: Equine, Standardbred filly, 8 days of age.

History: The filly was presented with a 5-6 day history of patent urachus, bloody urine, and a bloody vaginal discharge. Left fetlock lameness was observed on the day of euthanasia.

Gross Pathology: Suppurative osteomyelitis and periostitis with osteolysis and necrosis of bone and cartilage of the left rear cannon bone, with extension into the fetlock joint (suppurative arthritis), were observed. A patent urachus with chronic fibrinopurulent and necrotizing omphalitis with fibrosis was also present. The right rear cannon bone had a well-demarcated focus of thickened distal physeal cartilage along the dorsal and medial aspect, which resulted in a cartilaginous lesion 3mm in width and 2mm in depth, as compared to 1mm depth in the remaining physis.

Laboratory Results: None provided.

Contributor's Morphologic Diagnosis: Metatarsus: Focal retention of physeal cartilage with metaphyseal infraction.

Contributor's Comment: Evaluation of the distal right metatarsal bone was done for comparison with the severely affected left. Lesions in the right metatarsal were considered clinically incidental. The focal retention of growth cartilage in the right metatarsal bone (delayed endochondral ossification) is consistent with the gross lesions seen in the clinical entity of physitis/epiphysitis of horses[1,2]. Such lesions of focal retention of growth cartilage can be secondary to any lesion that would interrupt the vascular penetration of the growth plate such as trauma or inflammation, or represent primary lesions of cartilage maturation (dysplasia of osteochondrosis). In this case, the focal retention of growth cartilage is interpreted to be secondary to trauma with

infraction of primary trabecular bone. This interpretation is supported by the absence of cellular inflammation and the presence of irregularly arranged and fragmented cartilage cores (infractions) on the metaphyseal side of the lesion without presence of normal primary trabeculae. The presence of the cartilage cores indicates that cartilage mineralization and chondrocyte death had proceeded normally prior to lesion development. While trabecular infractions could be secondary to primary disorders of endochondral ossification, work in pigs has suggested that infractions are common causes of focal failure of endochondral ossification[3].

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AFIP Diagnosis: Metatarsus: Retained physeal cartilage, focal, with infraction of primary trabeculae, Standardbred, equine.

Conference Comment: Conference attendees discussed two possible pathogeneses for this lesion. The first is failure to resorb physeal cartilage, resulting in retention of the physis and a microenvironment prone to fractures. The second is an acquired problem, most likely trauma. Regardless of the cause, the end result is disruption of the vascular supply to the metaphyseal-diaphyseal junction. Invasion of capillary loops through the transverse septa and into the tubes of mineralization surrounding the hypertrophied chondrocytes of the growth plate is essential for modeling of the primary spongiosa. The absence of these vessels (secondary to fractures and fibrosis) results in failure to model and mineralize the growth plate and culminates with retention of cartilage within the growth plate (i.e. formation of "cartilage cores"). Like the contributor, conference attendees speculate that the latter pathogenesis is more likely.

Discussion focused on the cut back zone at the proximal metaphysis, where primary and secondary trabeculae are remodeled to form cortical bone. Cortical bone is normally decreased or absent in this area due to physiological remodeling, so the thin cortical bone should not be misinterpreted as pathologic. Another physiologically normal change is the chondrification of blood vessels in the growth plate. After crossing the growth plate, blood vessels normally undergo thrombosis and chondrification, so this also should not be misinterpreted as a pathologic change.

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CASE II - 02-13490 (AFIP 2889976)

Signalment: 4-month-old, male, Suffolk, *Ovis aries*, ovine.

History: The lamb was born with kyphosis, and as the animal grew, he developed a "Roman" nose that became progressively more pronounced and angular limb deformities that worsened over time. At the time of presentation and euthanasia, the lamb had extreme difficulty walking and required special care and feeding. The lamb's twin was born with no musculoskeletal abnormalities and remained healthy.

Gross Pathology: The lamb was in good nutritional condition. The dorsal aspect of the skull and nose was rounded (Fig. 1). The distal aspect of the pelvic limbs had moderate to severe valgus deformity (Fig. 2). The thoracic limbs, especially the left thoracic limb, had mild varus deformity (Fig. 3). There was mild scoliosis and kyphosis of the vertebral column. The ventral aspect of the ribs, from the costochondral junctions to the sternum, and the sternum were flattened and bowl-shaped. On longitudinal section of the sternum, the sternum was undulating (Fig. 4) and the fourth and sixth sternebrae were replaced by multiple small pieces of bone surrounded by thick cartilage. The articular cartilage of the occipital condyles and atlas was roughened, dull, gray, and pitted. The occipital condyles were elongated (Fig. 5), and there was increased angulation of the occipital condyles. The width of the intercondyloid notch was decreased. On saggital section of the vertebrae, sternebrae, the occipital condyles, and the long bones of the left rear leg, the physes were irregular with multiple ossification centers and islands of cartilage in the primary and secondary cancellous bone (Fig. 6), cyst-like structures, and occasionally hemorrhage. There were no significant gross lesions in the thoracic viscera, abdominal viscera, or brain.

Laboratory Results: Postmortem radiographic examination of the sternum, skull and limbs was performed. The sternebrae were misshapen, misaligned and of irregular sizes (Fig. 7). The skull exhibited pronounced rounding of the dorsal silhouette (Fig. 8). The hind limbs had valgus deviation centered at the metatarsophalangeal joint (Fig. 9). There appeared to be widening of the physis of the distal metatarsal bone with areas of bony proliferation. Areas of radiolucency were consistent with multiple centers of ossification and the diagnosis of spider lamb syndrome.

Contributor's Morphologic Diagnosis: Vertebrae and long bones: Chondrodysplasia.

Contributor's Comment: Your section may have two vertebrae with an intervertebral joint or a section of a long bone. The physes of the vertebrae and long bones are multifocally widened by multiple islands of cartilage resulting in multiple ossification centers (Fig. 10). These islands of cartilage extend into the primary and secondary cancellous bone (Fig. 11) and occasionally the cortex. The islands of cartilage consist

of disorganized clusters and rows of chondrocytes suspended in a chondroid matrix (Figs. 12, 13). The chondroid matrix is irregularly replaced by osteoid. There is occasional degeneration and necrosis of the islands of cartilage.

Spider lamb syndrome (ovine hereditary chondrodysplasia, spider lamb chondrodysplasia) is an autosomal recessive inherited trait in Suffolk and Hampshire sheep and their crossbreds[1,2]. A spectrum of gross lesions have been identified and include the following: tall lambs that are finely boned and poorly muscled with abnormally long legs and small heads, scoliosis, kyphosis, sternal deformities, a "Roman" nose, deviation of the nose, angular limb deformities, and, in all affected lambs, elongation of the occipital condyles leading to a decrease in the width of the intercondylar notch. Microscopically, there is nodular thickening of the cartilage in the centers of endochondral ossification in affected bones. This leads to multiple small ossification centers that may still be present in the metaphysis and impinge on the cortex. Occasionally, the affected cartilage can undergo degeneration. Irregularities of the cartilage columns in the ossification centers can occur.

The exact defect leading to spider lamb syndrome (SLS) is not known at this time. The abnormality has been localized to the distal end of ovine chromosome 6, and a defect in the gene encoding fibroblast growth factor receptor 3 (FGFR3) is believed to be the cause of SLS[3]. Fibroblast growth factor receptor 3 is included in a family of polypeptide receptors that contain a pair of cytoplasmic tyrosine kinase domains, three immunoglobulin-like domains, and a transmembrane domain.

Three types of human dwarfism (achondroplasia, hypochondroplasia, and thanatophoric dwarfism) are caused by mutations in FGFR3 [4,5], and mice lacking FGFR3 develop skeletal overgrowth and deafness[6]. Fibroblast growth factor receptor 3 is believed to be involved in the down regulation of chondrocyte growth in bone development[3,4,6,7,8]. The FGFR3 mutation in human dwarfism is believed to result in the continual activation of FGFR3 [4,8], while mutations disrupting the function of FGFR3 in mice result in excessive proliferation of chondrocytes in the physis and skeletal overgrowth[6,7].

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AFIP Diagnosis: Vertebra (per contributor), bone and growth cartilage: Chondro-osseous dysplasia, diffuse, with osteopenia, Suffolk, ovine.

Conference Comment: The contributor provided a thorough discussion of spider lamb syndrome. Other congenital skeletal malformations in lambs may be caused by maternal ingestion of plant teratogens or administration of drugs during certain stages of gestation.

Ingestion of locoweed (*Astragalus* sp. or *Oxytropis* sp.) by pregnant ewes may cause arthrogryposis and limb rotation in lambs. Overdosing pregnant ewes with the anthelmintic parbendazole may cause compression or fusion of vertebral bodies and

proximal ribs, curvature of long bones, and hypoplasia of articular surfaces in the lamb.[1] Ingestion of *Veratrum californicum* (skunk cabbage) by the dam around day 14 of gestation causes congenital cyclopean deformities, but other defects may occur depending on stage of gestation at plant ingestion. Ingestion around day 29 may cause shortening of metatarsal, metacarpal, and tarsal bones, medial bowing of forelimbs at the fetlock, and arthrogryposis.[1,9]

A syndrome known as bent-leg, or bowie, has been associated with ingestion of *Trachymene glaucifolia* (wild parsnip) by pregnant ewes in Australia and New Zealand. This disease affects the long bones of the forelimbs of lambs, causing flexion and lateral rotation of the knee joints and medial or lateral rotation of the fetlock joints. This has been reproduced experimentally by feeding a diet low in both calcium and phosphorus. Supplementation of the diet with phosphorus seems to reduce the incidence of disease.[1,9]

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CASE III – 10629/93 (AFIP 2890204)

Signalment: 6-week-old Norwegian elkhound, female, canine.

History: Two out of four puppies in a litter were unable to move normally. These clinical signs appeared at an age of 3 to 4 weeks and deteriorated rapidly within the next couple of weeks. They were sacrificed at an age of 6 and 8 weeks, respectively. Autopsy of one of them revealed a skeletal disorder as the cause of the problems. The same parents produced a new litter where two out of four puppies developed the same clinical signs as in the two first cases. One normal and the two diseased puppies in this litter were sacrificed. The sections submitted are from one of the affected animals.

Gross Pathology: The chest cavity showed a conspicuous flat appearance with a marked reduction of the distance between the ventral part of the spine and the chest bone. Costochondral junctions were prominent. The costochondral reduction on the ribs was very prominent and consisted of a soft chondroid tissue. The limbs were moderately shorter than normal. The epiphyseal part of the tubular bones was enlarged with a club-like appearance. Cut sections through these areas revealed a soft chondroid tissue containing a bony core markedly reduced in size. The skull had a normal size. The length of the vertebral column was not reduced although a moderate increase of chondroid tissue was observed around the endplates.

Laboratory Results: The clinical chemistry revealed no abnormalities consistent with the skeletal deformities. All the values recorded in the puppies of the second litter were otherwise within normal limits.

Contributor's Morphologic Diagnosis: Chondrodysplasia.

Contributor's Comment: Chondrodysplasia in the Norwegian elkhound was originally described by Bingel and Sand in 1982.[1] These dogs had disproportionately short limbs where the front limbs might appear relatively shorter than the hind limbs. The body trunk was also shorter than normal. Histological examination revealed a disorganized endochondral ossification and a zone of chondrocyte proliferation, which was decreased in width. Chondrocytes in all zones contained inclusions. This type of chondrodysplasia appeared to be inherited as an autosomal recessive trait.[2] It may be added that the ability of these dwarfs to walk and stand was only slightly affected.

   This description discloses both clinical and pathological differences from those demonstrated in the puppy of the present material. The age level of affected animals, the severity of the clinical signs and the type and distribution of macroscopical and microscopical lesions reveal that the present case represents a new type of chondrodysplasia in the elkhound.

Louw described in 1983 [3] chondrodysplasia in a litter of Bulldogs with some of the clinical and macroscopical features described in this case. More details regarding the puppies were, however, not reported.

A review of the morphological lesions in human skeletal dysplasia by Sillence et al. 1979 [4] reveals four disorders with significant lesions in the resting (reserve) zone. Hypercellularity in this zone as well as in other zones of the growth plate seem to be a conspicuous finding in two of them called achondrogenesis type 1 and 2. Enlarged and vacuolated chondrocytes with a reduced amount of intercellular matrix together with a disorganization of the endochondral ossification were also observed in these cases. The type 2 of achondrogenesis seems to be the most interesting disorder from a comparative point of view as it also has macroscopical and radiological findings which in many respects are similar to those observed in the elkhound puppy.

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AFIP Diagnosis: Long bone (site not specified), growth and articular cartilage: Chondrodysplasia, diffuse, with osteopenia, Norwegian Elkhound, canine.

Conference Comment: A differential diagnosis in dogs and cats with skeletal lesions and dwarfism should include lysosomal storage diseases. English Springer Spaniels with GM_1 gangliosidosis, a deficiency of beta-galactosidase, develop dwarfism, irregular intervertebral spaces, and degenerative articular changes in the femur and tibia. Mucopolysaccharidosis I (MPS I) is reported in Plott hounds and domestic shorthaired cats, causing facial and skeletal dysmorphia, corneal clouding, and cardiac valve insufficiency. Animals with MPS I have a deficiency in alpha L-iduronidase resulting in excess urinary excretion of heparin sulfate and dermatan sulfate. Mucopolysaccharidosis VI occurs in Siamese cats and manifests as skeletal abnormalities, including short stature, large paws, and facial dysmorphism. Affected cats have deficient activity of N-acetylgalactosamine 4-sulfatase and excrete dermatan sulfate in their urine. In animals with MPS VI, stored mucopolysaccharides stain metachromatically with toluidine blue stain. There is no metachromatic staining of cells in animals affected by MPS I.[1,5,6]

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CASE IV - P128-03 (AFIP 2892973)

Signalment: 11 months, neutered male, domestic shorthaired cat, "Tacos", feline.

History: Bilateral fractures of caput femoris, epiphyseal/metaphyseal border. No known trauma.

Radiology: Both columns of femur have inhomogenous decreased radiopacity, indicating lytic areas. Malalignment and a radiolucent line through the physis of both femoral heads indicate bilateral physeal fracture in the region. Both femoral heads have homogenous bone opacity. The mineralization in the skeleton appears normal with no sign of osteopenia. In conclusion, bilateral "Salter Harris-type" fractures with lytic changes in the column and no signs of osteopenia. Resection of the femoral heads was done and the specimens were sent for PAD.

Gross Pathology: The specimen comprised two femoral heads, both with a thick synovial membrane attached. Areas of dull frayed articular cartilage covering the periphery close to the synovial membrane attachments and part of the central femoral head could be seen.

Laboratory Results: None reported.

Contributor's Morphologic Diagnosis: Femoral head, bone necrosis and fibrous reactive tissue at the epiphyseal/metaphyseal border, remnants of growth plate cartilage, focal areas of fraying of articular cartilage, synovitis, chronic, proliferative, pannus-like, slipped capital femoral epiphysis, developing pseudoarthrosis, "spontaneous femoral capital epiphyseal fractures in the cat."

Contributor's Comment: Microscopically the femoral head is characterized by reactive fibrous tissue together with bone necrosis and remnants of the growth plate (the growth plate in the cat should close between 8-10 months of age). A synovitis with pannus-like properties was also found.

The lesions have similarities with slipped femoral epiphysis, Legg-Calve-Perthes disease, canine metaphyseal osteopathy, traumatic fracture of the femoral neck and osteomyelitis. However, the description of femoral neck metaphyseal osteopathy in the

cat[2] is most compatible with the radiographic and microscopic lesions described above and these authors suggested a new idiopathic disease in cats.

Recently, similarities between "spontaneous femoral capital epiphyseal fracture"[1] and feline metaphyseal osteopathy have been discussed. It has been suggested that the metaphyseal osteopathy is a pseudoarthrosis formation following a spontaneous femoral capital epiphyseal fracture. The predominance of neutered male cats has led to the suggestions that a delay in closure of the growth plate and an immature vascular supply could predispose to the fractures[2].

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AFIP Diagnosis: Femoral head, physis/subphysis: Fracture, with fibrosis, woven bone formation, and synovial hyperplasia (callus), domestic shorthair, feline.

Conference Comment: Conference attendees discussed the paucity of cells relative to the thickness of the growth plate and that it may indicate delayed closure. The irregularity of the growth cartilage at the deep margin was determined to be a true change, based on separation and necrosis of the physeal cartilage and the presence of fibrous tissue growing perpendicular to the growth plate. Changes in the synovium include synoviocyte hyperplasia, and synovial hyperplasia and hypertrophy. Some slides demonstrate articular cartilage erosion.

It has been suggested that femoral capital physeal fractures may be a result of physeal dysplasia or delayed growth plate closure. The high proportion of gonadectomized cats noted in the literature supports the association with delayed growth plate closure and resulting increased susceptibility to spontaneous fracture. High body weight has been identified as an additional risk factor in these cats.[1]

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