Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2022-2023

Conference #24 **26 April 2023**

CASE I:

Signalment:
13-day old male Holstein calf (*Bos taurus).*

History:
This male Holstein calf was unable to stand since birth. There were increased lung sounds and bilateral nasal discharge. There was asymmetry in the right tuber coxae. Radiographic changes suggested congenital unilateral hip dysplasia.

Gross Pathology:
The calf was in good body condition with symmetrical muscle mass but was smaller than normal. The umbilical stump is dry.

The joint capsule of the right coxofemoral joint is thickened up to 2 cm by tough white fibrous tissue and gelatinous or clear to yellow fluid. Within the joint capsule are thick mats of yellow-tan friable material resembling fibrin. The synovial fluid is yellow and less viscous than normal. The cartilage of the femoral head is dull and irregular with a punctate to moth-eaten appearance. There is gelatinous thin strands of fibrin with focal hemorrhage within the left stifle and right tarsal joint. The rest of the body was normal.

Laboratory Results:
No aerobic or anaerobic bacteria were isolated from the hip joint. The joint capsule was positive for *Ureaplasma* sp by PCR

Microscopic Description:
The tissue on this slide includes joint capsule with synovial membrane, femoral head with articular epiphyseal cartilage complex, epiphysis, physeal cartilage and metaphysis. Within the wall of the joint capsule are aggregates of neutrophils and macrophages with high-protein fluid including fibrin. There is fibrous tissue surrounding these areas. The synovial membrane has villus formation and synoviocytes are hypertrophied and up to 3 cells thick.

There is fibrin with neutrophils beneath the synovial membrane at the transition zone, the junction between joint capsule and perios-

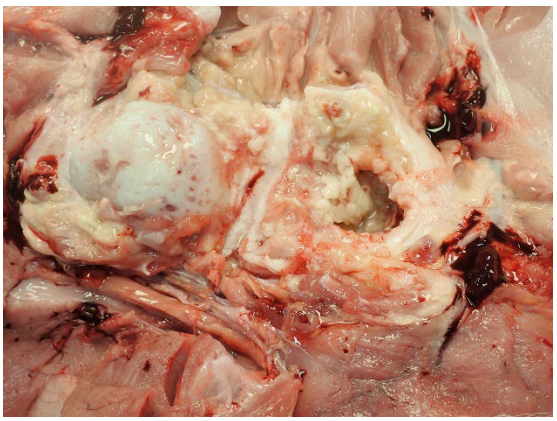

Figure 1-1. Joint, calf. The joint capsule of the right coxofemoral joint is thickened and fibrotic up to 2 cm. and contains thick mats of fibrin. The synovial fluid is yellow and less viscous than normal. The cartilage of the femoral head is dull and irregular with a punctate to moth-eaten appearance. (Photo courtesy of: Department of Pathobiology, Ontario Veteirnary College, University of Guelph, Guelph, Ontario, Canada; https://ovc.uoguelph.ca/pathobiology).

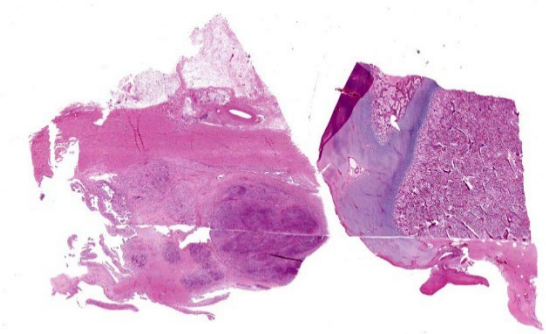

Figure 1-2. Joint, calf. One section of markedly thickened joint capsule (left) and the femoral head are submitted (right). (HE, 5X)

teum. The articular epiphyseal cartilage complex is mostly normal however within the epiphysis is a region of fibrosis and connective tissue replacement of hematopoietic marrow of the intertrabecular spaces. Some of this fibrous tissue has mature collagen.

Contributor's Morphologic Diagnoses:
Osteomyelitis of femoral head, neutrophilic and histiocytic fibrosing joint capsulitis/periarthritis and synovial hyperplasia.

Contributor's Comment:
The history, diagnostic imaging findings, gross pathology findings and histopathology indicates this is a congenital infectious arthritis and osteomyelitis. The identification of *Ureaplasma* confirms this as fetal infection and arthritis with *Ureaplasma diversum*. This is an uncommon manifestation of *Ureaplasma* infection, which is better known for inducing amnionitis and fetal pneumonia with large lymphoid follicles around bronchi. The location of the reaction in the coxofemoral joint is typical of this entity.

Contributing Institution:
Department of Pathobiology, Ontario Veterinary College, University of Guelph,
Guelph, Ontario, Canada
https://ovc.uoguelph.ca/pathobiology/

JPC Diagnosis:
Coxofemoral joint: Arthritis, pyogranulomatous and proliferative, diffuse, severe, with osteomyelitis and articular cartilage necrosis and erosion.

JPC Comment:
In large animals, neonatal polyarthritis is commonly the result of systemic infection secondary to omphalophlebitis and/or failure

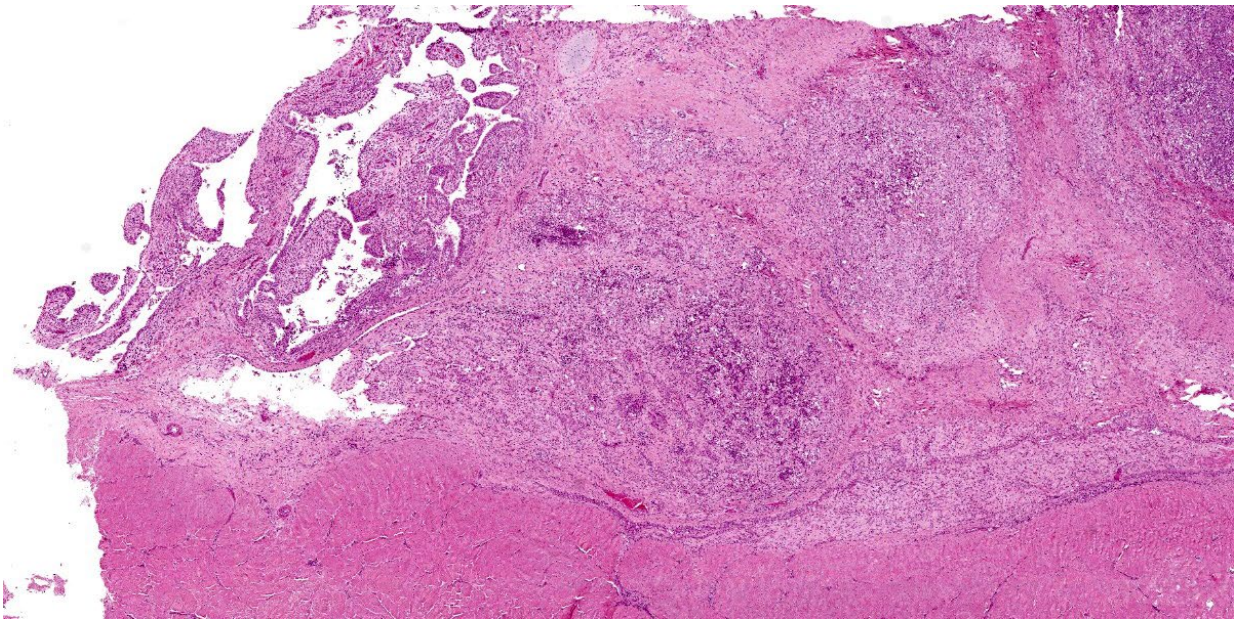

Figure 1-3. Joint capsule, calf. There are prominent synovial villi (left) and the joint capsule is expanded by marked inflammation and fibrosis (right). (HE, 25X)

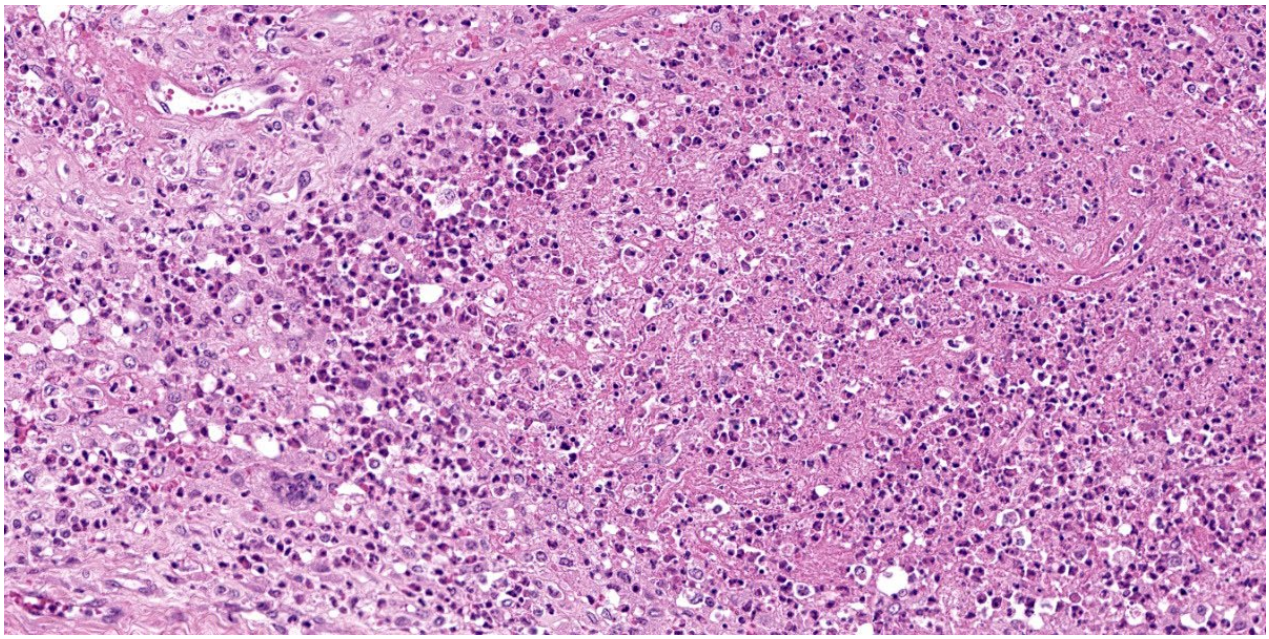

Figure 1-4. Joint capsule, calf. Areas of necrosis within the joint capsule are infiltrated by large number of viable and necrotic neutrophils, macrophages, and rare multinucleated giant cell macrophages. (HE, 272X)

of passive transfer with subsequent immunodeficiency. In calves, the most common organisms associated with neonatal polyarthritis are coliforms and streptococcus. Both agents result in systemic lesions, including fibrinosuppurative meningitis and polyarthritis. *Streptococcus* septicemia also characteristically causes embolic iridocyclitis with hypopyon and corneal clouding.[3]

Another important differential for polyarthritis in calves is *Mycoplasma bovis*¸ which belongs to the same order as *Ureaplasma*.[3] *M. bovis* causes a variety of diseases in cattle including pneumonia, mastitis, otitis media in calves, and polyarthritis.[3] Calves are infected by consuming the bacterium in the milk of infected cows and often develop concurrent pneumonia. Histologically, affected joints have fibrinosuppurative and erosive arthritis with synovial hyperplasia.[3]

Ureaplasma diversum differs from these neonatal infections as infection in calves begins *in utero*. *U. diversum* is a common commensal organism found in the nasal passage and male and female reproductive tracts of cattle.[6] The bacteria is transmitted by coitus and as a major cause of reproductive loss in cattle.[5] It causes urogenital infections such as vaginitis and endometritis in cows and seminal vesiculitis in bulls.[6] Pregnant cows infected with virulent strains may have third trimester abortions or give birth to weak or stillborn calves.[5] The bacterium causes necrotizing placentitis and mild arteritis which affect the amnion more severely than the chorioallantois.[5] Aborted calves are well preserved and fetal membranes may be retained. Calves may have erosive conjunctivitis and

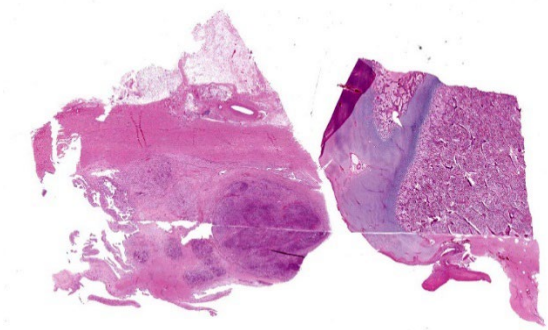

Figure 1-5. Femoral head, calf. There is a focal area of medullary fibrosis within the femoral epiphysis. (HE, 72X)

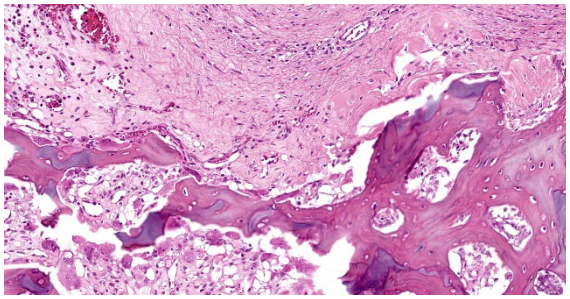

Figure 1-6. Femoral head, calf. There is osteoclastic remodeling of boney trabeculae at the edge of the area of epiphyseal fibrosis. (HE, 72X)

nonsuppurative alveolilis.[5] Interstitial pneumonia in a calf due to *U. diversum* was recently seen in WSC, year 2021-2022, Conference 24, Case 2; readers are encouraged to review that case for a full histologic picture of the infection in calves.

This case illustrates another sequela to *U. diversum* infection in utero: severe erosive polyarthritis[3,4]. The infection may affect one or multiple joints and tends to target the coxofemoral joint, shoulders, elbows, stifle, and carpal and tarsal joints.[3,4] In affected joints, articular surfaces are deformed, with irregularly thinned cartilage and extensive granulation tissue that extends into the subchondral bone.[3,4]

One last differential to consider for severe polyarthritis in calves is *Chlamydia pecorum.* Infection may occur due to ingestion of the bacteria or in-utero infection.[3] Virulent strains of this obligate intracellular bacteria spread from the intestine via portal circulation to the liver and then systemically were it ultimately finds the joints.[3] Affected animals are febrile, depressed, and reluctant to move.[3] In addition to severe polyserositis and meningoencephalitis, there is severe serofibrinous arthritis with edema and petechiation in the adjacent soft tissue.[1,3]

Conference participants discussed the quality of the primary and secondary spongiosa in this section. The thin, delicate spicules that with retained cartilage cores led some conference participants to consider osteogenesis imperfecta as a secondary process. According to the history provided by the contributor, this animal was never able stand, so participants also considered disuse osteopenia as a potential cause for these findings.

References:

1. Cantile C, Youssef S. The nervous system. In: Maxie MG, ed. *Jubb, Kennedy and Palmer's Pathology of Domestic Animals*. Vol 1. 6th ed., Philadelphia, PA: Elsevier Ltd.; 2016:391-392.
2. Carli SD, Dias ME, da Silva M, Breyer GM, Siqueira FM. Survey of beef bulls in Brazil to assess their role as source of infectious agents related to cow infertility. *J Vet Diagn Invest.* 2022;34(1): 54-60.
3. Craig LE, Dittmer KE, Thompson KG. Bones and Joints. In: Maxie MG, ed. *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals.* Vol 1. 6th ed. St. Louis, MO: Elsevier; 2016: 154.
4. Himsworth CG, Hill JE, Huang Y, Waters EH, Wobeser GA. Destructive polyarthropathy in aborted bovine fetuses: a possible association with Ureaplasma diversum infection? *Vet Pathol*. 2009; 46(2): 269-72.
5. Schlafer DH, Foster RA. Female Genital System. In: Maxie MG, ed. *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals.* Vol 3. 6th ed. St. Louis, MO: Elsevier; 2016:399-402, 411-416.
6. Strait EL, Madsen ML. Mollicutes. In: McVey DS, Kennedy M, Chengappa MM, eds. *Veterinary Microbiology.* 3rd ed. Ames, IO: Wiley Blackwell. 283-292.

CASE II:

Signalment:

12-year-old, male, mixed breed, dog (*Canis familiaris*)

History:
Left shoulder pain for 1 year. Radiographs show marked proliferation of bone around the shoulder joint involving, among other, the glenoid cavity, the head of the humerus and the greater tubercle. The limb was amputated.

Gross Pathology:
The specimen received was approximately 15cm in diameter. It was rigid and consisted of bone covered with muscle, tendons and connective tissue. Normal anatomic landmarks, including the joint, were not identified. The specimen was sliced transversely and sampled in several areas.

Laboratory Results:
No laboratory findings reported.

Microscopic Description:
Near the outer surface of the bone there is an elongate cystic structure in the wall of which there are several variably sized nodules of low cellularity composed of spindle and stellate cells with small hyperchromatic nuclei and thin and long cytoplasmic processes floating in optically empty spaces. The nodules are surrounded by fibrous tissue and/or more densely packed neoplastic tissue. In

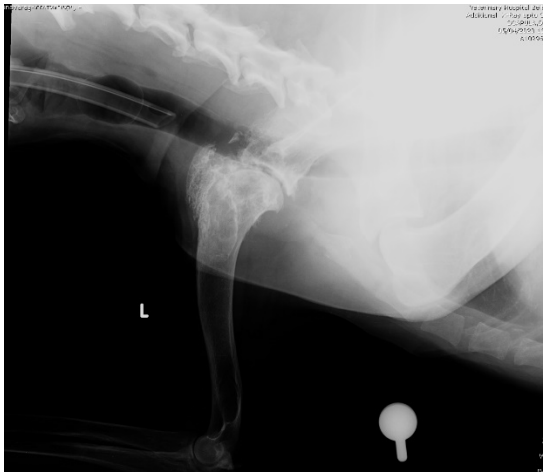

Figure 2-1. Scapulohumeral joint, dog. Pre-amputation radiographs demonstrate marked proliferation of bone around the shoulder joint involving, among other, the glenoid cavity, the head of the humerus and the greater tubercle. (Photo courtesy of: The Weizmann Institute of Science; http://www.weizmann.ac.il/)

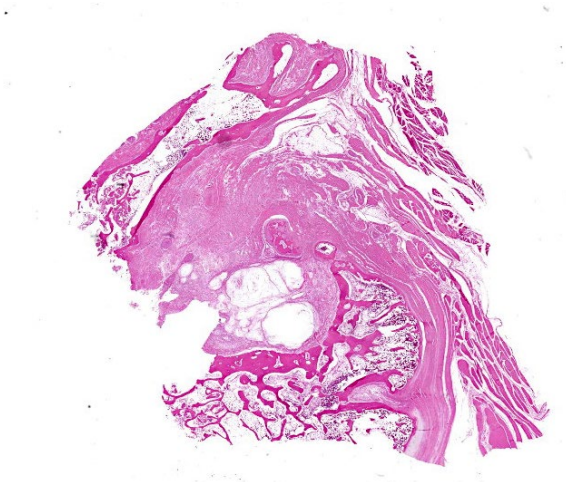

Figure 2-2. Scapulohumeral joint, dog. One section of the scapulohumeral joint with the joint capsule and humeral head is submitted for examination. (HE, 6X)

The nodules form an aggregate near the outer surface of the bone. Mitotic figures are rare. In both slides, the undulant contour of adjacent bone suggests compression by the proliferative tissue and there is probable osteophyte formation (bone islands away from the bulk of the bone). Polygonal cells of uncertain identity are attached to the inner aspect of the pseudocyst.

Contributor's Morphologic Diagnoses:
Synovial myxoma

Contributor's Comment:
Synovial myxoma is the most common benign neoplasm in the joints of dogs.[3] Its microscopic appearance is characteristic but because it is an uncommon tumor 86% of cases in one report were initially diagnosed as malignant.[1] The tumor typically consists of variably sized nodules composed of a low number of stellates to spindle cells surrounded by abundant hypovascular myxoid matrix.[1,3]

The findings in a series of 39 cases indicate that large breed, middle-aged dogs, especially Doberman Pinschers and Labrador retrievers were commonly affected, and the stifle and digits were the most common sites. Survival times were long (average >2.5

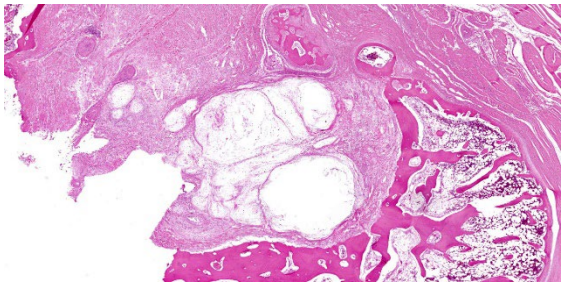

Figure 2-3. Scapulohumeral joint,dog. The joint space and is expanded by a multilobular mass with abundant clear myxomatous stroma. (HE, 6X)

years) even with incomplete excision. Three of 39 cases had local recurrence, but none metastasized or directly resulted in death.[1] Whilst some cases are confined to the joint capsule, others are infiltrative and grow along fascial planes. This appears to be the case in the submitted slides in which the tumor is located near bone and not within the joint. In the series of 39 cases, bone invasion was seen in 8 dogs. The authors concede that bone invasion is not typical of benign tumors, but their rationale to use the same diagnosis for all cases was the similarity of the histologic features of the tumors, irrespective of the presence of bone invasion.[1] Cases without bone lysis or expansion outside the joint capsule can be treated with synovectomy. Of cases confined to the joint capsule and treated with synovectomy, 10% recur.[3] Cases with bone lysis cause significant pain and usually require amputation.[3]

The viscous fluid produced by these tumors suggests that they originate from type B (fibroblast-like) synoviocytes which produce synovial fluid,[1] but this remains unproven as there are no reliable markers for this cell[2] and the IHC results in the case series cited above showed significant positive staining for CD18, which is a marker for type A synoviocytes.[1]

Previous designations of this entity include myxoma of the synovium – the term used for this entity when it was first described by RR Pool in 1990 (in the 3rd edition of Meuten's *Tumors in Domestic Animals*), myxosarcoma and nodular synovial hyperplasia.[3]

The submitted case is unusual in involving the shoulder, which was not affected in any case of the large case series.

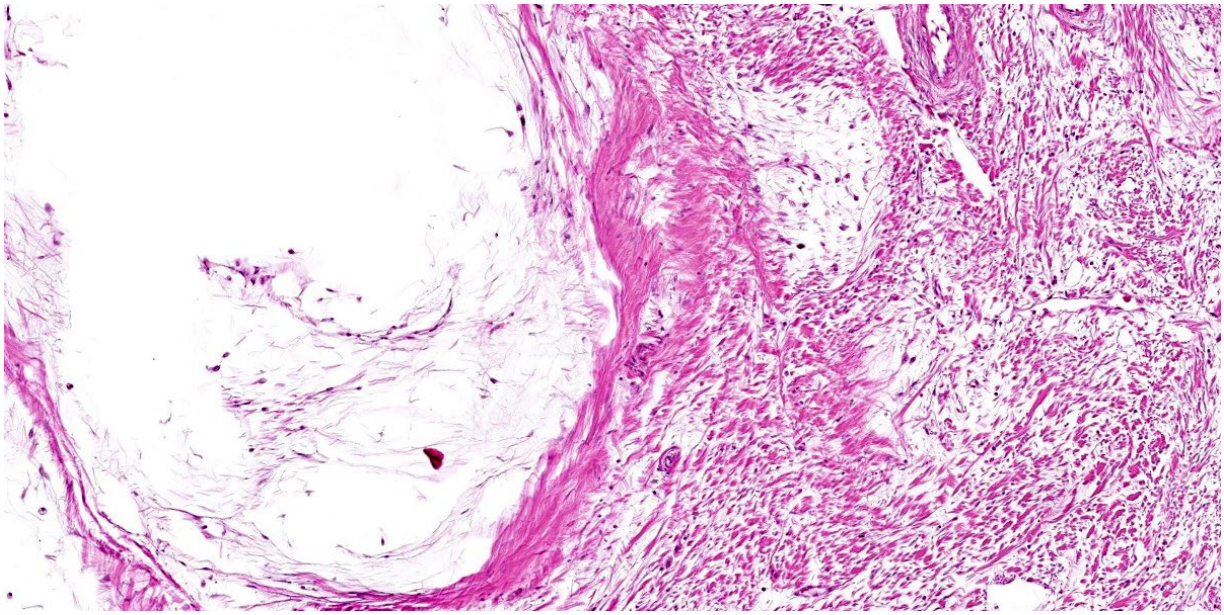

Figure 2-4. Scapulohumeral joint, dog. There is a large lobule of the neoplasm, a smaller developing nodule, and more diffuse infiltration of the joint capsule (right). (HE, 17X)

The three most common tumors of the canine synovium are histiocytic sarcoma, synovial cell sarcoma, and synovial myxoma, with widely divergent prognosis. Because bone invasion may be present in synovial myxoma, the 3 tumors cannot be differentiated radiographically. Synovial myxoma can be identified by its characteristic histologic appearance. Immunohistochemistry can be used to differentiate synovial histiocytic sarcoma (cytokeratin negative, CD18 positive) – the most common malignant tumor from the synovial cell sarcoma (cytokeratin positive, CD18 negative), which is a controversial entity in animals.[1,2]

Contributing Institution:
The Weizmann Institute of Science
http://www.weizmann.ac.il/

JPC Diagnosis:
Joint capsule: Synovial myxoma.

JPC Comment:
A few reports of synovial myxomas with atypical presentations in dogs have been reported. Izawa et al describe a synovial myxoma with intramuscular infiltration as an incidental finding in a 16-year-old dog that was euthanized due to progressive renal failure. The dog had no clinical signs of lameness, and the tumor was only described when a jelly-like substance was discovered between skeletal muscles of the hind limb on necropsy.[4] There were also multiple small translucent nodules in the stifle. Histologically, the nodules had the classic appearance of a synovial sarcoma, with few spindle to stellate cells embedded in abundant myxoid matrix, and similar nodules were identified in the jelly-like areas between muscles.[4]

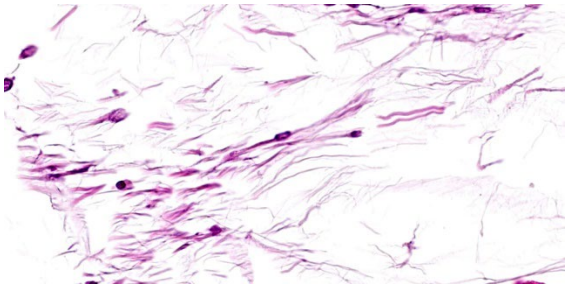

Figure 2-5. Scapulohumeral joint, dog. Neoplastic cells are spindled with long processes and pink vacuolated cytoplasm. (HE, 710X)

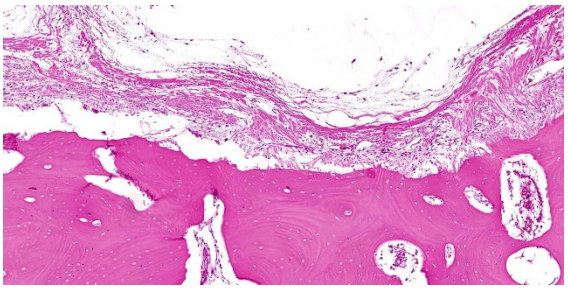

Figure 2-6. Scapulohumeral joint, dog. There is scalloping of the humeral cortex in apposition to the neoplasm as a result of remodeling due to pressure. (HE, 103X)

Neary et al described a synovial myxoma associated with the cervical articular facet in a 12-year-old mixed breed dog. The animal presented with a two-week history of progressive neurologic deficits and tetraparesis, and the dog was successfully treated with a dorsal hemilaminectomy and facetectomy.[6]

Synovial myxomas were recently described in cats as well. In a 2020 *Vet Pathol* article, Craig et al described synovial cystic and myxomatous lesions in 16 cats. Most (12) of the masses were located in the elbow, and in all cases, the masses were unilateral. Three cats had masses composed of cysts; two cats had masses composed of spindle cells on myxomatous matrix (myxoma); and 11 cats had a combination of cysts and myxoma. While most of the lesions increased with time, the lesion was not the cause of natural death or euthanasia in any of the cats. Since the majority of the cats in this study also had bilateral degenerative joint disease, the authors hypothesized that synovial cysts initially form due to increased articular pressure and herniation of synovium; myxomas then

form when there is subsequent neoplastic transformation.[2]

A single report of a synovial myxoma has been published in a 5-year-old rabbit. The affected hind limb was amputated, and grossly, the neoplasm partially effaced the femur and stifle joint, elevating the patella and extending into the fascia between muscles. Histologically, the neoplasm had the classic features of myxoma and was frequently surrounded by reactive bone, fibrosis, or cartilage. The authors recommended using the term "infiltrative" as part of the diagnosis for such invasive tumors to provide a better description of the biologic behavior.[5]

References:

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2. Craig LE, Kirmer PM, O'Toole AD. Synovial Cysts and Myxomas in 16 Cats. *Vet Pathol.* 2020; 57(4): 554-558.
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CASE III:

Signalment:
2 years and 6 months old female Holstein Friesian Cow (*Bos taurus).*

History:
The cow was euthanized due to a large (41.5cm circumference), round, firm, ulcerated mass with embedded incisors at the rostral aspect of the mandible. Whilst the cow was unable to hold saliva, she was still able to eat and drink with some adaptation.

Gross Pathology:
A very large (160x140x160 mm), expansile, broad based, firm, pink to red mass extends from the dorsolingual aspect of the rostral mandible, displacing teeth 301, 302, 401, 402, 403 and 404 laterally. Approximately 70% of the surface of the mass is ulcerated.
On cut surface, the mass exhibits a central 60x24x16 mm cavity which contains approximately 15 ml of clear, yellow tinged, watery fluid surrounded by cream to yellow to pale pink, variably soft to very firm, gelatinous to fleshy tissue. Where the mass merges with

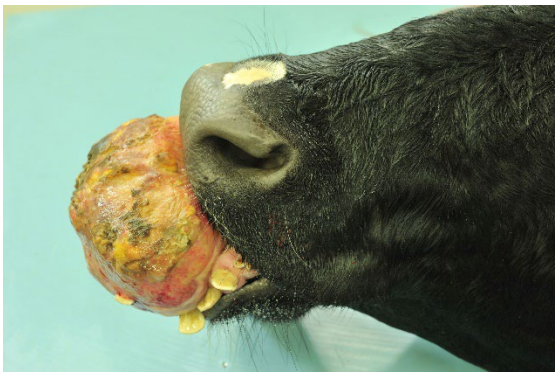

Figure 3-1. Mandible, ox. A 1.6 cm expansile, broad based neoplasm extends from the dorsolingual aspect of the rostral mandible, displacing teeth 301, 302, 401, 402, 403 and 404 laterally. (Photo courtesy of: Division of Pathology, Public Health and Disease Investigation Veterinary Diagnostic Services, School of Veterinary Medicine, College of Medical, Veterinary and Life Sciences, University of Glasgow (Garscube Campus) 464 Bearsden Road, Glasgow G61 1QH, Scotland, https://www.gla.ac.uk/schools/vet/cad/)

regular mandible, the mandible is thickened to a maximum thickness of 69 mm.

The forage in the forestomaches, particularly the rumen, is excessively long.

Laboratory Results:
No laboratory findings reported.

Microscopic Description:
Mandibular mass: The section contains parts of a large and moderately cellular mass which comprises loosely to moderately densely and haphazardly arranged, very vague bundles and streams of neoplastic cells, situated in and supported by a moderate to large amounts of multifocally mildly oedematous, fine collagenous stroma, interspersed with numerous elongated, partially anastomosing bony spicules and trabeculae arranged in parallel to one another and perpendicular to the superficial surface. The bone trabecules are lined by a largely one cell (ranging up to three cells) thick layer of polygonal to elongate cells with eosinophilic/mildly basophilic cytoplasm and round to oval nuclei with finely stippled to clumped and marginated chromatin (osteoblasts). The neoplastic cells are

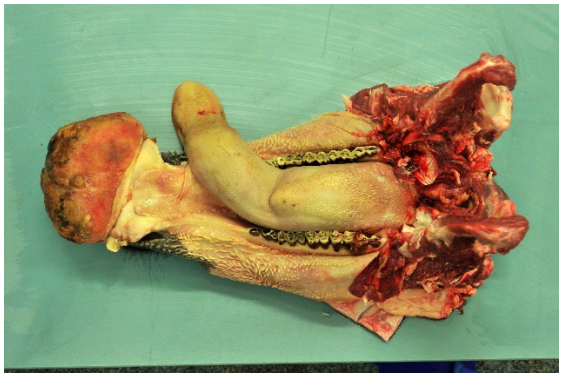

Figure 3-2. Mandible, ox. Dissected specimen of this mandibular neoplasm (Photo courtesy of: Division of Pathology, Public Health and Disease Investigation Veterinary Diagnostic Services, School of Veterinary Medicine, College of Medical, Veterinary and Life Sciences, University of Glasgow (Garscube Campus) 464 Bearsden Road, Glasgow G61 1QH, Scotland, https://www.gla.ac.uk/schools/vet/cad/)

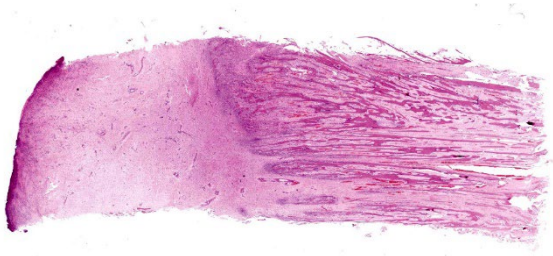

Figure 3-3. Mandible, ox. One section of undecalcified maxilla is submitted for examination. The mass is composed of spindle cells and fibrous matrix separated by parallel trabeculae of unmineralized mature woven bone. (HE, 6X)

spindle-shaped to stellate-shaped with moderately defined cell boundaries and small amounts of eosinophilic cytoplasm. Their nuclei are irregularly oval with finely stippled to mildly clumped, commonly also marginated chromatin and one or two, small basophilic nucleoli. Anisocytosis and anisokaryosis are mild, very small numbers of binucleated cells are present and less than one mitotic figure is seen in 10 high power fields. Mitotic figures, however, are more evident in those regions close to bone formation and at the interface between bone and collagenous tissue, where also a substantial increase in cellularity is evident.

The mucosa is diffusely ulcerated, and covered by fibrin, eosinophilic and basophilic cellular debris and large numbers of viable and degenerate neutrophils, in deeper levels admixed with small numbers of macrophages, lymphocytes and plasma cells which in turn are situated amongst plump fibroblasts vaguely orientated parallel to the surface and small vessels lined by hypertrophied endothelial cells orientated perpendicular to the superficial surface (granulation tissue formation).

Very small numbers of lymphocytes, plasma cells and macrophages are diffusely distributed throughout the neoplastic population and commonly also seen forming very small aggregates in perivascular location.

Contributor's Morphologic Diagnoses:
Mandible, rostral aspect: Ossifying fibroma, bovine, *Bos taurus.*

Contributor's Comment:
Ossifying fibromas (OF) are benign, proliferative, intraosseous lesions with a rapid growth rate and strong predilection for the mandible.[3,17] OF are most frequently recognized in human beings and young horses (<1 year old)[8], but have also been described in dogs[2,3,6,7], cats[3], sheep[3], and rarely cattle.[13,19] Additionally, individual cases of OF are published in a range of other species including a canary[14], a rabbit[19], a llama[5], roe deer[21] and a cynomolgus monkey[15].

In humans OF are most commonly found in the posterior mandible, although maxillary and zygomatic lesions are also recognized.[4] The rostral mandible represents a clear predilection site in young horses (where the condition also is known as *equine juvenile mandibular ossifying fibroma*)[8], and also in ruminants and domestic carnivores[3,13,14]. Additional reported sites include long bones[3,14], equine paranasal sinuses[12], the equine proximal phalanx[1], the canine os penis[7] and the canine zygomatic arch.[2] Reported cases in cattle are restricted to the mandible (although paucity of cases may underlie a lack of recognition of atypical locations).[13,14]

In humans, a predilection for ossifying fibromas has been established in females in their

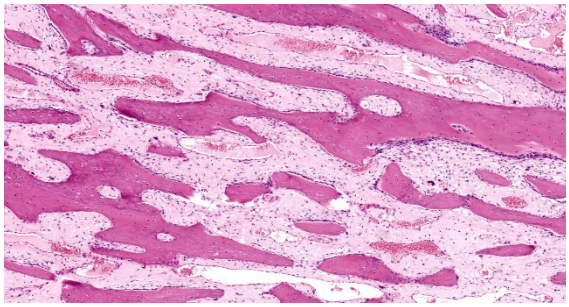

Figure 3-4. Mandible, ox. Higher magnification of trabeculae of mature woven bone lined by a single layer of quiescent osteoblasts. (HE, 117X)

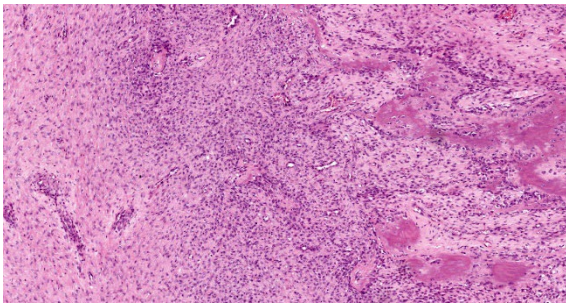

Figure 3-5. Mandible, ox. The leading edge of the mass is densely cellular. (HE, 57X)

30s or 40s.[4] In contrast to this, equines exhibit such lesions most commonly in young animals (<12 months)[8], whilst no clear age-related predilection is reported for other species at present (possibly again due to paucity of cases). No sex predisposition is currently reported in animals.

Human OF are reported to be non-painful. Their most significant effects are of malocclusion and cosmetic impairment.[4] Similarly, the primary effects of OF in domestic animals are impaired occlusion and/or prehension as well as a predisposition to pathologic fractures.[3,8,13,14] The further effects of OF in atypical locations are largely due to their space-occupying behavior and specific effects dependent on the location in question, for example urethral obstruction in the case of an OF in the os penis.[1,2,7,12]

Histologically ossifying fibromas are characterized by spindle shaped fibroblasts interspersed with trabeculae of woven bone which are surrounded by a rim of osteoblasts.[17] Historical miscategorisation and underreporting of OF in the literature is suspected, owing to the similarity between osteoma and OF and the disagreement about the existence of a disease continuum between fibrous dysplasia (FD) and OF.[17,18] Currently, histological differentiation of OF from FD is largely based on the presence of a rim of osteoblasts surrounding foci of woven bone.[7,8,10,18,19,20] Osteomas can be distinguished from OF by their grossly sessile or pedunculated appearance

arising from the surface of the bone, their containment within the periosteal membrane, relative hypocellularity and the presence of lamellar bone with bone marrow, whilst osteosarcomas can be differentiated from OF by the pleomorphism and a considerably higher mitotic rate of the neoplastic population with osteoblasts typically also filling the intertrabecular spaces rather than only lining the bony trabecules.[7,8,12,18,19,20]

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JPC Diagnosis:
Bone, mandible: Ossifying fibroma.

JPC Comment:
As the contributor describes, ossifying fibromas are rare in cattle, and since this case was submitted to WSC, another report of three cases of mandibular ossifying fibromas in cattle was published in *Journal of Comparative Pathology.* All cases were characterized as well demarcated and projected from the rostral mandible, where they replaced or displaced multiple incisors. Histologically, the neoplasms had the characteristic features of ossifying fibroma: trabeculae of bone lined by osteoblasts surrounded by haphazardly arranged neoplastic spindle cells with invasion, degeneration, and necrosis of adjacent bone.[11] In one case, the neoplastic spindle cells were confluent with the periodontal ligament, and some have speculated that ossifying fibroma of the mandible may originate

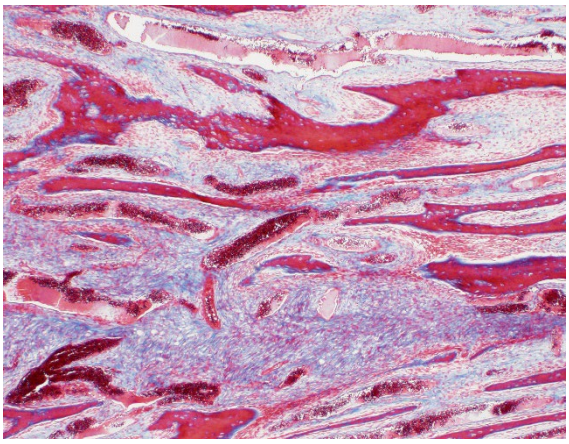

Figure 3-6. Mandible, ox. A Masson's trichrome highlights the collagen in the intertrabecular spaces. (Masson's trichrome, 400X)

from pluripotent stem cells of the periodontal ligament.[11]

Ossifying fibroma is also rarely reported in marine (striped mullet) and freshwater fish (sauger and walleye). The freshwater fish cases were linked to pollution from a mining operation. A single case of cutaneous osseous fibroma was more recently reported in the caudal peduncle of a tetra.[10] The neoplasm contained dysplastic ctenoid scales, and the authors theorize that the neoplasm may have originated from the bone in these scales, a theory which is in line with central ossifying fibromas in humans, which also originate from bone.[10]

Historically the presence or absence of a rim of osteoblasts around trabeculae of woven bone was used to differentiate ossifying fibroma (OF) from fibrous dysplasia (FD). Recent work, however, has demonstrated that both OF and FD can have osteoblasts around trabeculae. Alternatively, both OF and FD may lack an osteoblastic rim around trabeculae. For these reasons, the presence or absence of an osteoblastic rim is no longer considered diagnostically useful. The degree of bone differentiation histologically, and the sharpness of demarcation radiographically are generally considered the most useful features in distinguishing OF and FD. OF has

well differentiated woven bone histologically, and sharply defined margins radiographically. FD may have poorly differentiated bone that is difficult to recognize as bone (ie "proto-bone") histologically, and is poorly delineated with ill-defined margins radiographically. Both OF and FD arise from the intra-osseous region and can have multinucleated giant cells (osteoclasts). As these represent a spectrum of benign, fibro-osseous lesions, it may be challenging to impossible to definitively differentiate OF from FD without the use of radiographs.[8,16]

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CASE IV:

Signalment:
19 months old, female, mixed-breed (*Sus scrofa domesticus*) domestic pig.

History:
The pig was from a small farm housing pigs and other animals, including one boar and four sows that farrowed 23 piglets. After birth, the piglets were divided into four pens containing piglets of the same size from different sows. The number of piglets in each pen were as follows: pen 1, 8 piglets; pen 2, 4 piglets; pen 3, 9 piglets; and pen 4, 2 piglets. All pigs were fed a diet of boiled corn bran and millet; however, only the piglets in pen 3 became ill. At 10 months old, the first clinical signs appeared in the piglets, and their condition progressively worsened. Initially, the piglets presented with respiratory distress and underdevelopment. Later, they developed bilateral swollen face, mainly in

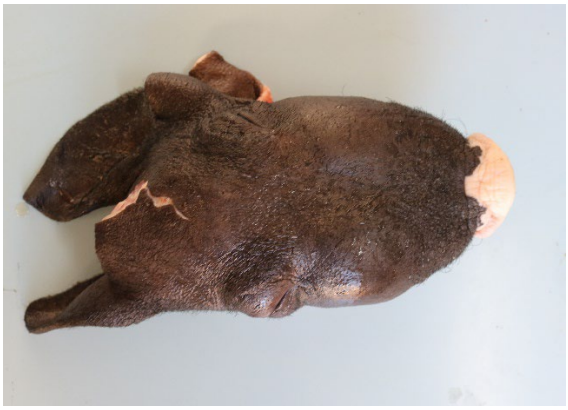

Figure 4-1. Maxilla, pig. There is marked bilaterally symmetrical expansion of the maxilla. (Photo courtesy of: Laboratório de Patologia Veterinária, Faculdade de Medicina Veterinária, Universidade Federal de Mato Grosso, Brazil)

the maxilla, partial mouth opening and protruding tongue, difficulty in food retention and mastication, loss of general body condition, and dyspnea. Subsequently, all pigs in pen 3 died under these conditions.

Gross Pathology:
One piglet was euthanized and underwent necropsy. Marked bilateral enlargement of the facial bones, predominantly in the maxilla, was observed. These were easily sliced using a knife and the section surfaces were observed to be pale. The nasal cavity lumen decreased due to thickening of the maxillary bones. The teeth were loose, and the molars were lingually tipped. In addition, the ribs were soft and broke effortlessly under pressure. Most of the long bones showed epiphyseal plate thickening, and the trabecular structure was poorly visible.

Laboratory Results:
No laboratory findings reported.

Microscopic Description:
Histopathological examination of the mandible and maxilla revealed accentuated diffuse proliferation of soft and irregular fibrous conjunctive tissue, which was evaluated by Masson's trichrome staining around the osteoid trabeculae, many of which were

partially or completely demineralized, as observed on von Kossa staining. Osteoclasts forming multinucleated cells were observed in the surface grooves (Howship's lacunae) in the mineralized trabeculae or clustered within the connective tissue. Histological changes were not observed in the renal parenchyma or parathyroid gland.

Contributor's Morphologic Diagnoses:
Face bones, maxilla: osteolysis, diffuse, severe fibroplasia (fibrous osteodystrophy), domestic pig (*Sus scrofa domesticus*)

Contributor's Comment:
Bone growth and maturation are complex processes involving an interaction between genetic factors, local and systemic hormones, dietary nutrients, and mechanical forces. Any factors interfering with the synthesis of proteoglycans or collagen by chondroblasts or osteoblasts, differentiation of precursor cells, or resorption of bone by osteoclasts can result in skeletal abnormalities. The expression of an abnormality depends on many factors, including the phase of skeletal development that is altered, severity of the defect, age of the animal at the time of insult, and persistence of the influencing factor. Thus, the range of possible skeletal defects is large and a single cause can develop several different manifestations[5].

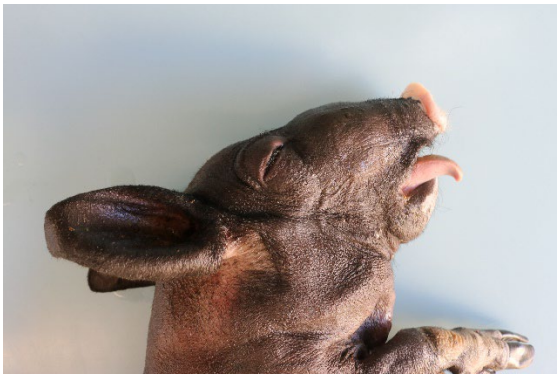

Figure 4-2. Maxilla, pig. There is marked bilaterally symmetrical expansion of the maxilla. (Photo courtesy of: Laboratório de Patologia Veterinária, Faculdade de Medicina Veterinária, Universidade Federal de Mato Grosso, Brazil)

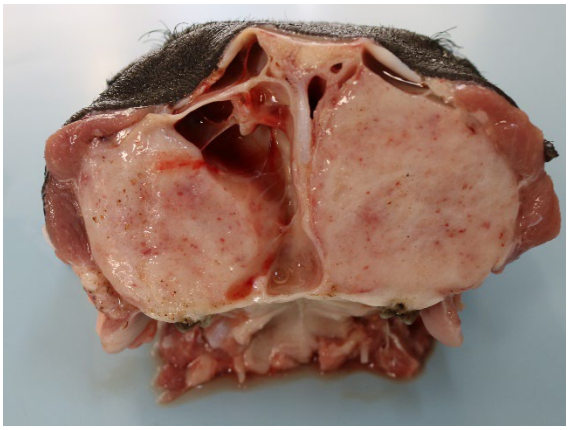

Figure 4-3. Maxilla, pig. The maxilla cut easily with a knife. There is marked bilaterally symmetrical expansion of the maxilla with encroachment on the nasal cavity. (Photo courtesy of: Laboratório de Patologia Veterinária, Faculdade de Medicina Veterinária, Universidade Federal de Mato Grosso, Brazil)

Understanding the regulation of phosphorus and calcium levels in the animal body is necessary to comprehend the pathogenesis of bone lesions. Most mediators involved in calcium phosphorus homeostasis have evolved in fish, although their roles are repurposed during adaptation to land environments. Thus, while susceptibility to vitamin D deficiency in vertebrates can be traced back to fish, the specifics of its manifestation as a disease show both similarities and differences to what is observed in humans. Calcium and phosphorus are strictly regulated in all animals because of their vital roles in numerous cellular functions. During the colonization of land, vertebrates transitioned from a sea environment that was comparatively richer in calcium than phosphorus to a land environment, with a six- fold higher gravity force, that was poor in calcium and relatively richer in phosphorus. This led to the evolutionary changes involving major adaptations in bone structure and calcium/phosphorus regulation. These adaptations included a highly efficient system for intestinal calcium absorption and flexible bone remodeling, which allowed the use of bones as an internal reservoir of calcium to compensate for variations in dietary intake[14].

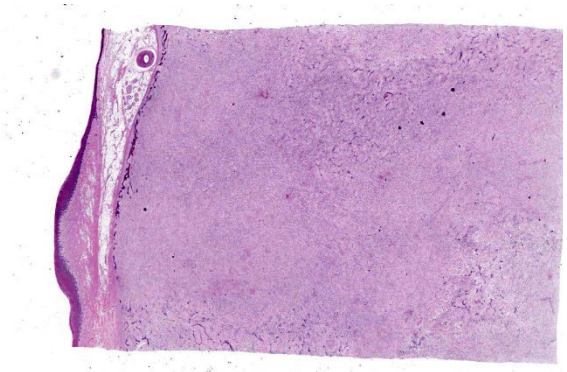

Figure 4-4. Maxilla, pig. A single section of the mass is submitted for examination. There is marked resorption of the cortex of the bone. (HE, 6X)

Deficiencies in calcium, phosphorus, and vitamin D disrupt bone conditions, resulting in a group of diseases known as osteodystrophies or metabolic bone disease. In the field of veterinary medicine, this is a broad term denoting pathological conditions affecting multiple bones. Osteodystrophies are most frequently caused by genetic, nutritional, and/or hormonal abnormalities that affect bone growth, modeling, or remodeling, typically through disruptions in calcium/phosphorus metabolism. Calcium and phosphorus are required for a variety of essential bodily functions in addition to those involved in skeletal development. The skeleton is composed of approximately 99% of calcium and 85% of phosphorus in the body. There are three distinct forms of calcium and phosphorus in the body: ionized, protein-bound, and complex atoms in extracellular fluids (including plasma). The ionized fractions of these minerals (Ca2+ and HPO42-) are physiologically active and are strictly regulated by the parathyroid hormone (PTH), 1,25- dihydroxyvitamin D (1,25[OH]2D3), calcitonin, and phosphatonin system[5,6,9,14].

PTHs are secreted by the parathyroid gland when calcium-sensing receptors on chief cells detect low serum ionized calcium concentrations. The net effect of PTH increases plasma ionized calcium levels and reduces plasma phosphate concentrations. The PTH induces the renal tubules to open the calcium channel, allowing increased resorption of calcium from the renal filtrate and increased breakdown of phosphate channels. Consequently, the resorption of phosphorus from the renal filtrate decreases. In the bone, high PTH concentration results in the recruitment and activation of osteoclasts, leading to increased osteoclastic bone resorption and release of calcium and phosphorus in the circulation[5].

Vitamin D exists in two forms: vitamin D2 (ergocalciferol), obtained from yeasts and plants and vitamin D3 (cholecalciferol), obtained from the diet or as an end product of the skin photochemical reaction of 7-dehydrocholesterol, which explains why sun exposure increases vitamin D levels in most species. Latitude, time of day, season, and level of skin pigmentation can affect the vitamin D3 production in the skin. At lower angles, the sun does not have the requisite intensity to produce vitamin D in the skin. Furthermore, high levels of melanin in the skin absorb ultraviolet photons, making it unavailable for vitamin D synthesis. A dense hair/wool coat also reduces cutaneous vitamin D3 synthesis. Dogs and cats are an exception in mammals in that they do not produce vitamin D in the skin, owing to the presence of an enzyme that breaks down 7-dehydrocholesterol, making it unavailable for conversion to vitamin D. Therefore, cats and dogs are reliant on dietary vitamin D.

Vitamin D2 from the diet and vitamin D3 from the skin/diet are transported to the liver, where they form 25-hydroxyvitamin D (25OHD), the major form of vitamin D in the circulation. Therefore, serum 25OHD concentration reflects the level of cutaneous vitamin D3 formation and/or dietary levels of vitamin D. Serum 25OHD levels are measured to determine whether an individual has

adequate or deficient vitamin D status. The most active form of vitamin D is 1,25-dihydroxyvitamin D, which is formed in the renal proximal tubular epithelial cells. This step is closely regulated and 1,25(OH)2D3 production is directly stimulated by high PTH and low phosphorus levels, and indirectly by low ionized calcium, which acts via PTH. When plasma phosphorus and ionized calcium concentrations are adequate and PTH levels are low, 25OHD is converted to inert metabolites during the initial step of the degradation pathways. Active vitamin D binds to the nucleus of the renal tubular and intestinal epithelial cells, resulting in increased absorption of calcium and phosphorus from the kidneys and intestine, inhibition of PTH production in the parathyroid gland, and negative feedback to decrease its own production[5,6,14].

Calcitonin is secreted by thyroidal C cells in response to increased serum ionized calcium concentrations. It inhibits osteoclast action leading to decreased osteoclastic bone resorption, and subsequent decrease in the release of calcium and phosphorus into the blood, allowing normalization of serum ionized calcium levels[5].

Recently, many phosphatonins have been found to be involved in phosphorus metabolism, the most important of which is the fibroblast growth factor 23 (FGF23). FGF23 is produced by osteocytes in the bone and its production is increased by either hyperphosphatemia or increased 1,25(OH)2D3. The kidney is the main target organ of FGF23; together with its cofactor klotho, FGF23 downregulates phosphorus channels in the kidney, resulting in decreased resorption of phosphorus from the renal tubules. FGF23 also decreases the production of 1,25(OH)2D3 by inhibiting the enzyme that acts in its formation and activates the enzyme that catabolizes 1,25(OH)2D3. in the parathyroid gland, FGF23 decreases secretion of PTH. FGF23 activity results in decreased plasma phosphorus concentration[5].

Metabolic bone diseases can occur when these regulatory mechanisms do not work in harmony. Metabolic bone diseases include rickets, osteomalacia, fibrous osteodystrophy, or osteoporosis; these distinct morphological entities have characteristic pathogenesis and lesions. Nonetheless, specific diagnosis is difficult in many cases, as multiple conditions may be present, especially in those induced by nutritional deficiencies. This means that cases reported in the literature should be scrutinized, and only those confirmed by histopathology should be considered definitive[5,6,14].

Fibrous osteodystrophy (osteodystrophia fibrosa, osteitis fibrosa cystica) is a relatively common metabolic bone disease characterized by extensive osteolysis, accompanied by proliferation of fibrous tissue and poor mineralization of the immature bone. The pathogenesis involves primary or secondary hyperparathyroidism with persistently elevated

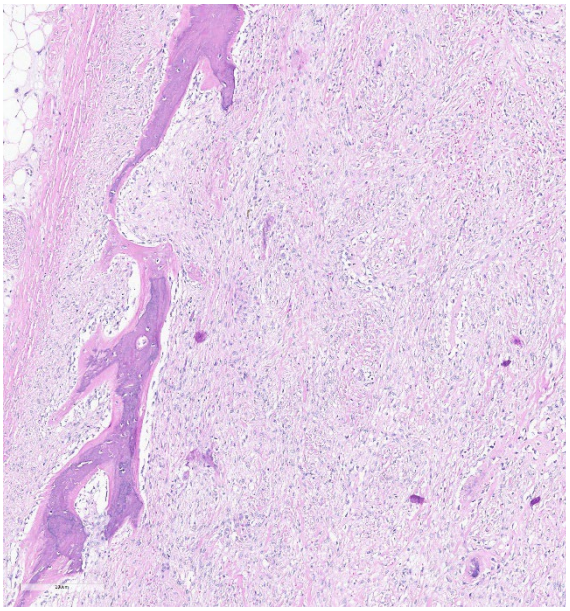

Figure 4-5. Maxilla, pig. Higher magnification of the resorbed cortex. (HE, 110X)

plasma PTH levels causing bone resorption, resulting in skeletal alterations. The susceptibility of different animal species to fibrous osteodystrophy varies, as does the distribution of lesions. Horses, pigs, dogs, cats, ferrets, dromedary camels, guinea pigs, reptiles, New World nonhuman primates, and goats are commonly affected, but the disease is rare in sheep and cattle[1,4,5,6,9,12,13].

Primary hyperparathyroidism, typically caused by functional parathyroid gland adenoma, leads to an increase in PTH levels. Parathyroid gland adenocarcinoma and hyperplasia, although reported, are rare[3,5]. Generalized bone resorption can also occur because of paraneoplastic syndrome (pseudohyperparathyroidism or hypercalcemia of malignancy) when tumors produce calcitropic hormones that act similarly to parathyroid hormones[2].

Secondary hyperparathyroidism is a much more frequent cause of fibrous osteodystrophy in animals than primary hyperparathyroidism and may stem from either chronic renal disease, or a dietary imbalance of calcium and phosphorus. PTH secretion is stimulated by a reduction in plasma ionized calcium, whatever the cause, and if the stimulus persists, generalized bone resorption results[5].

Renal hyperparathyroidism occurs predominantly in small animals as a complication of chronic renal failure, most often in dogs and occasionally in cats. This alteration often referred as renal osteodystrophy, has recently been renamed “chronic renal failure–mineral and bone disorder” (CKD-MBD) in humans and veterinary medicine. Renal osteodystrophy may occur in dogs with CKD; however, the manifestations of uremia are usually more severe than those of skeletal lesions. Impaired glomerular filtration in renal failure leads to progressive hyperphosphatemia

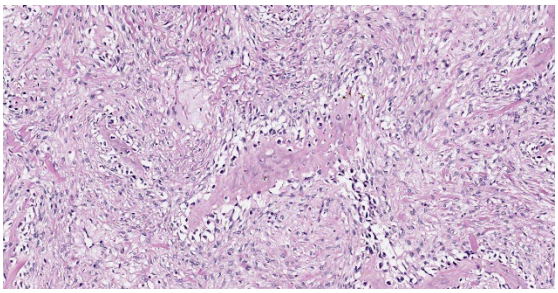

Figure 4-6. Maxilla, pig. Within the fibrous matrix replacing the bone, there are irregular trabeculae of woven bone lined by a single layer of vacuolated osteoblasts. (HE, 400X)

caused by reduced renal clearance of phosphate, causing hypocalcemia because of the inverse relationship between plasma ionized phosphate and calcium concentrations. Hyperphosphatemia also triggers the production of FGF23 by osteocytes, exacerbating hypocalcemia, as FGF23 functions to decrease the production of 1,25(OH)2D3 due to inhibition of the enzyme that acts in the formation and activates the enzyme that catabolizes 1,25(OH)2D3. Persistent hypocalcemia stimulates PTH release, resulting in osteoclastic bone resorption[4,5,7].

Nutritional hyperparathyroidism while frequently noted in horses, is reported sporadically in other species, mainly in young, rapidly growing animals. This condition is generally caused by diet containing low calcium and a relatively high concentration of phosphorus, or in association with vitamin D deficiency. Vitamin D deficiency alone can cause rickets or osteomalacia, but reduced calcium absorption from the intestine in animals combined with vitamin D deficiency often results in concurrent fibrous osteodystrophy. Excess dietary phosphorus may cause fibrous osteodystrophy even in animals receiving adequate dietary calcium. Increased plasma phosphate concentrations, resulting from increased intestinal absorption of phosphorus, depresses plasma ionized calcium and indirectly stimulates the release of PTH. In all species, several factors influence the

development and severity of lesions in secondary hyperparathyroidism. These include the degree to which dietary calcium is deficient and, perhaps more importantly, the degree to which dietary phosphorus is in excess. This condition usually occurs after ingesting unsupplemented diets consisting largely of grain, corn, and grain byproducts, such as bran, for some months, hence the term bran-disease[1,5,8,9]. In dogs and cats, nutritional hyperparathyroidism is often caused by diets that consist largely or entirely of meat or offal, as the calcium content of such diets is low, and the calcium to phosphorus ratio is very high. Additionally, in horses, fibrous osteodystrophy occurs in animals grazing on tropical grasses high in oxalate; even though dietary calcium and phosphorus are normal, oxalate binds calcium making it unavailable for absorption. Several grasses, including *Setaria sphacelata, Cenchrus ciliaris, Brachiaria mutica, B. humidicola, Digitaria decumbens, Pennisetum clandestinum, P. purpureum, and Panicum spp.,* contain sufficient oxalate to produce clinical disease[5,14].

The clinical signs and gross lesions of fibrous osteodystrophy generally develop more rapidly in young, growing animals because of their increased rates of bone synthesis and remodeling. Early signs include minor changes in gait, stiffness, transient and shifting lameness, and lassitude. Loss of appetite with progressive cachexia and decreased growth develops later. Affected animals frequently show bilateral enlargement of the bones of the skull, affecting both the maxillae and mandibles, hence the term big-head. Bony enlargement begins along the alveolar margins of the mandible, producing cylindrical thickening and reducing the intermandibular space. The molar margins of the maxillae subsequently begin to enlarge, and the enlargement spreads to involve the palate, remainder of the maxillae, and lacrimal and zygomatic bones. Initially, the enlargements were soft and could be cut using a knife. Involvement of the palate reduces the nasal passage and may cause dyspnea. Palatine and mandibular thickening causes a reduction in the buccal cavity, impairing mastication. This causes teeth to loosen and get partially buried or exfoliate, and the softened bone causes pressure, further impairing prehension and mastication[1,5,9].

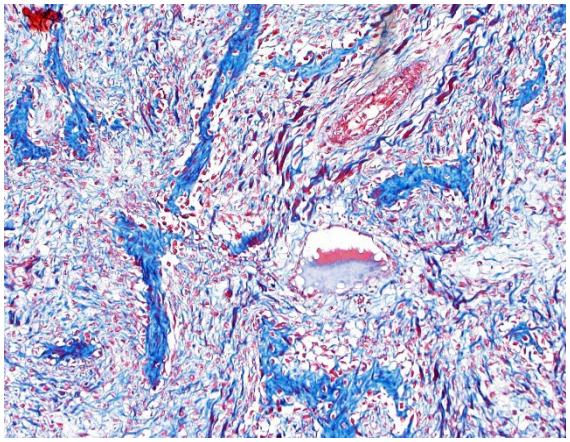

Figure 4-7. Maxilla, pig. A Masson's trichrome demonstrates the loosely arranged collagen in the intertrabecular spaces, and the collagen within trabeculae of woven bone. (HE, 100X)

The microscopic features of fibrous osteodystrophy are similar in all domestic animal species, and characterized by increased osteoclastic bone resorption, marked fibroplasia, and increased osteoblastic activity with the formation of immature woven bone. In early lesions, the increase in bone resorption is reflected by an increased number of active osteoclasts, often within Howship's lacunae along the surface of the trabeculae. Osteoblastic activity is also prominent, and it is not unusual to observe bone trabeculae resorption on one side, while new bone is being added to the other. Under physiological conditions, once osteoclasts have completed their required phase of resorption, they undergo apoptosis and disappear from the resorption sites. However, in fibrous osteodystrophy, groups of osteoclasts are fre-

quently found mixed with fibroblastic elements as PTH enhances osteoclast survival[1,5,9].

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JPC Diagnosis:
Jaw bone: Osteopenia, diffuse, severe, with marked fibroplasia (fibrous osteodystrophy).

JPC Comment:
The contributor provides an excellent review of the physiologic regulation of calcium and phosphorous and the pathologic manifestations of dysregulation of these minerals. Our scientific understanding of calcium and phosphorous metabolism began just over a century ago, but the descriptions of rickets date back millenia, with Roman physicians in the first and second century C.E. describing bowed legs and curved spines.[11] Beginning in the 17th century, there was a steady increase in the number of children afflicted by rickets (or English disease, as it was known at the time). In 1634, rickets was listed as the cause of death in 14 of 10,900 deaths in London, and extensive texts describing the clinical and gross features of rickets were published around 1650.[10,11] The association with lack of sunlight was first suspected by Polish physician Sniadecki in 1822, and in 1889, a map of cases in England revealed its association with industrialized cities, whose tall buildings and narrow streets blocked sunlight, and the seasonality of the affliction.[8,10] In the 20th century, it was estimated that up to 90% of the urban-dwelling children in Boston and Leiden suffered from rickets.[10,11]

In the early 20th century, our understanding of calcium and phosphorous metabolism began to grow. The first histopathologic description of rachitic bones was published by

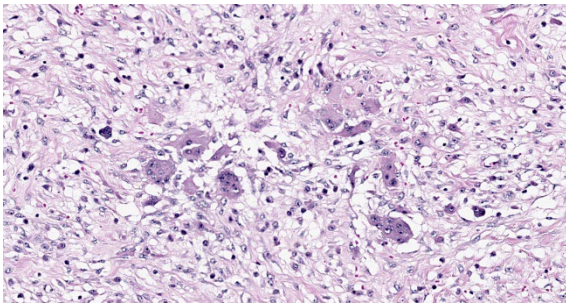

Figure 4-8. Maxilla, pig. Aggregates of osteoclasts are present in areas of previous mineralized bone resorption. (HE, 400X)

German physician and pathologist Christian Georg Schmorl in 1909, and in 1918, British biochemist Edward Mellanby successfully induced rickets in beagle puppies by feeding an oatmeal diet.[8,10] He further went on to cure the affliction by administering cod liver oil, a remedy used to prevent rickets in fishing villages.[8,10] Many suspected that the curative agent within cod liver oil was the fat soluble vitamin A. Elmer McCollum, who discovered vitamin B, hypothesized that a novel vitamin in cod liver oil possessed antirachitic properties; he proved this theory by demonstrating that cod liver oil still cured rickets even after aeration and heat destroyed the notoriously labile vitamin A.[8,10,11] Around the same time, it was demonstrated that UV light exposure prevented and treated rickets; and exposure of certain foods to the same UV radiation endowed that food with antirichitic properties.[8,10] Vitamin D2 and D3 were synthesized in the 1930s, and soon after, vitamin D supplementation of commercial foods and public awareness campaigns to increase sunlight exposure virtually eliminated rickets in industrialized nations.[8,10] It was not until 2004 that FGF23 was discovered, which filled in many of the gaps in our knowledge of phosphorous metabolism.[8]

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