Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2023-2024

Conference #15 — 10 January 2024

CASE I:

Signalment:
Four-year-old, male neutered Pygmy goat (*Capra aegagrus hircus*)

History:
This pygmy goat was presented to the Royal Veterinary College Farm Animal Hospital for further evaluation and possible treatment of an oral mass. Computed tomography (CT) of the head identified severe bony enlargement of the rostral aspect of both mandibles with destructive and lytic bony changes from the rostral margins of the mandible up to the first premolar bilaterally. Moderate soft tissue swelling surrounded the misshaped mandibles. The 402, 403, and 404 teeth were missing and the remaining incisors were displaced laterally. Surgical options were discussed with the owner but due to the extent of the lesion and the complexity of the surgical approach, the owner elected to euthanise the animal.

Gross Pathology:
Arising from the rostral mandible predominantly to the right of midline is a proliferative, dark red, moderately soft mass measuring 8x3x2.5cm with a bleeding surface. On sectioning, the mass is grey and solid. The mass displaces the five remaining incisors over to the left side and all the incisors are loose.

Figure 1-1. Mandible, goat. Arising from the rostral mandible, predominantly to the right of midline, is a dark, red mass measuring 8x3x2.5 cm. (*Photo courtesy of:* Dept of Pathobiology & Population Sciences, The Royal Veterinary College, https://www.rvc.ac.uk/pathology-and-diagnostic-laboratories)

Microscopic Description:
Rostral mandibular mass: Arising within the mandibular bone is an unencapsulated, moderately well demarcated, expansile, multinodular neoplasm which raises the contour of the gingival epithelium. The mass is composed of abundant multinucleated giant cells interspersed with a dense population of spindle shaped cells in a fibrovascular stroma. Each cell type represents approximately 50% of the cellular population in the section. The giant cells have well demarcated borders with abundant eosinophilic cytoplasm that contains varying numbers of microvacuoles, and between two and ten nuclei which are randomly distributed in the centre of the cell and have finely

Figure 1-2. Mandible, goat. The mass displaces the five remaining incisors over to the left side and all incisors are loose. (*Photo courtesy of:* Pathobiology & Population Sciences, The Royal Veterinary College)

stippled chromatin. The spindle-shaped cells are poorly defined with a moderate amount of eosinophilic fibrillar cytoplasm, elongate nuclei, and finely clumped chromatin. There is mild anisokaryosis and anisocytosis of both cellular populations. There are four mitoses detected in 10 HPF's (x400), three of which are bizarre mitoses. At the periphery of the neoplasm, there is fragmentation and necrosis of the mandibular bone and hyperplasia of osteoblasts. Occasional giant cells contain multiple pyknotic nuclei (apoptosis or individual cell necrosis). Multifocally, macrophages contain yellow to brown, globular pigment (haemosiderophages). The overlying gingival epithelium exhibits mild hyperplasia.

Contributor's Morphologic Diagnosis:
Mandible: Central giant cell granuloma (aggressive form).

Contributor's Comment:
Differential diagnoses for masses arising in the jaw which contain numerous giant cells include giant cell granulomas of the jaws, osteosarcoma (giant cell variant), osseous fibroma, or low grade spindle cell sarcoma with giant cells. The density of the giant cell population and the lack of osteoid or mineralized matrix is not consistent with the latter three differentials in this case.

Giant cell granulomas of the jaws are currently differentiated based on location into peripheral or central giant cell granulomas.[10] Peripheral giant cell granuloma (PGCG, previously known as giant cell epulis, peripheral giant cell tumor, osteoclastoma, reparatory giant cell granuloma, and giant cell hyperplasia of the oral mucosa) is a reactive and non-neoplastic gingival lesion that clinically presents as a soft to firm, polypoid or nodular lesion on the gingiva and alveolar ridge and is believed to originate from the periosteum or periodontal ligament.[1,5,6, 9, 10] There is minimal bone lysis associated with PGCG. These lesions, along with pyogenic granuloma and fibrous hyperplasia, are the most common reactive hyperplastic lesions in the oral cavity and have been described in humans, dogs, and cats.[1-3,6,11]

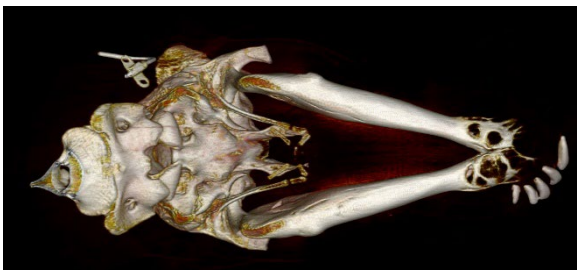

Figure 1-3. Mandible, goat. Computed tomography (CT) of the head identified severe bony enlargement of the rostral aspect of both mandibles with destructive and lytic bony changes from the rostral margins of the mandible up to the first premolar bilaterally (*Photo courtesy of:* Pathobiology & Population Sciences, The Royal Veterinary College)

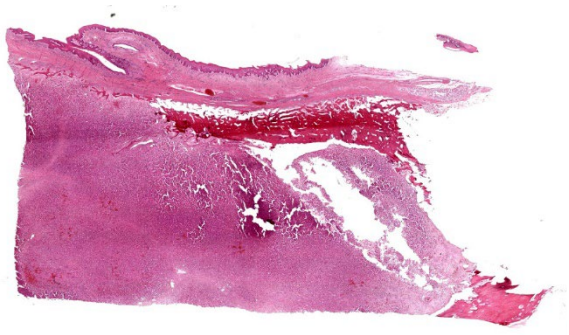

Figure 1-4. Mandible, goat. One section of a mass effacing the normal architecture of the mandible is submitted for examination. The mass is covered by an intact and slightly hyperplastic mucosa. (HE, 5X)

Central giant cell granuloma (CGCG), on the other hand, is a rare benign, non-metastatic, intraosseous lesion which is further subdivided into non-aggressive and aggressive forms based on its biological behavior. The former is associated with asymptomatic swelling and the latter associated with pain, cortical bone destruction, tooth root resorption, displacement of teeth, and a high recurrence rate.[7] Histologically, peripheral and central giant cell granulomas are characterized by variable numbers of multinucleated giant cells intermixed with a dense population of mononuclear spindle-shaped cells and variable amounts of collagenous matrix; however, CGCG may exhibit more foci of haemorrhage and occasional trabeculae of woven bone compared to PGCG.[7] Some investigators consider CGCG to be a variant of giant cell tumor of bone, which arise in the ends of long bones, and prefer the term 'giant cell lesion' with no distinction of granuloma.[6,11] One report in the literature describes a case of 'giant cell tumour' within the caudal mandible of a goat which also involved the temporomandibular joint.[4] CGCG in humans shows a female predilection (2:1) and is more common in the mandible than maxilla.[1] CGCG can also affect extragnathic bones, mainly in the craniofacial region.[10]

In this case, given the intraosseous location of the mass, the presence of osteolysis, displacement of the incisor teeth, and the lack of mineralized and osteoid matrix, a diagnosis of aggressive central giant cell granuloma was made.

The pathogenesis of CGCG is poorly understood and there is still dispute over whether this is a neoplastic or reactive lesion.[7] Giant cells within giant cell granulomas are thought to arise from osteoclasts and positive histochemical staining for tartrate-resistant acid phosphatase (TRAP), which is an enzyme unique to osteoclasts, and receptor activator of nuclear factor kappa B (RANK), which regulates osteoclast differentiation and activation, supports an osteoclastic origin for these masses.[2,3]

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The Royal Veterinary College
Hawkshead Lane, North Mymms
Hertfordshire, UK
https://www.rvc.ac.uk/

JPC Diagnosis:
Jaw: Giant cell tumor of bone.

JPC Comment:
The contributor provides an excellent overview of central giant cell granuloma (CGCG), an entity that is well-described in human literature. The World Health Organization defines CGCG in humans as "an intraosseous lesion consisting of cellular fibrous tissue containing multiple foci of hemorrhage, aggregations of multinucleated giant cells, and, occasionally, trabeculae of woven bone."[7] While this is an

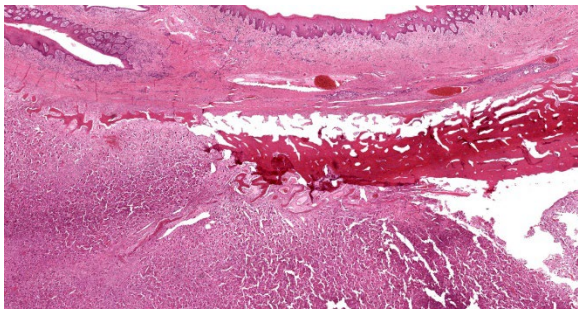

Figure 1-5. Mandible, goat. Higher magnification of the effacement of cortical bone by the mass. (HE, 18X)

apt description of the examined sections in this case, it could well describe several other types of bone tumors with a giant cell component, and differentiating among these entities remains challenging.

Given the paucity of reported veterinary cases, much of what is "known" about this tumor in veterinary species is extrapolated from human literature. Even within the human literature, CGCG remains a contentious entity as the pathogenesis is unknown and experts disagree on fundamental issues, such as whether CGCG is neoplastic or reactive, or whether the lesion is a single neoplastic lesion or a mix of neoplastic and reparative processes.[7] Many researchers also believe this entity is simply a giant cell tumor of bone in an uncommon location. What is fairly clear, however, is that the term "granuloma" is a misnomer, as the multinucleated giant cells are osteoclastic rather than macrophagic, as would be expected in a true granuloma.

The biologic behavoir of CGCG is difficult to predict. When surgical resection is elected, reported recurrence rates in humans vary between 11 and 49%.[7] The most consistent gross lesion present in aggressive CGCG is perforation of cortical bone; however, despite investigating myriad histologic parameters, no studies have identified reliable histologic features that can predict the course of disease.[7]

As an interesting side note, a key differential for CGCG in human medicine is cherubism, an autosomal dominant disorder characterized by bilateral expansion of the mandible and/or the maxilla which appears in the first few years of life.[7] The dysplastic fibrous tissue of the mandible and/or maxilla can extend into the orbital floor and is often accompanied by swelling of the submandibular lymph nodes. These changes cause a characteristic upward tilting of the eyes and fullness of the face, resulting in the cherubic expression that gives the condition its name.[12] Cherubism is yet another non-neplastic fibrotic lesion confined to the jaws that cannot be distinguished from other giant cell lesions of bone by histology alone.[12]

This week's conference was moderated by Dr. Linden Craig, Professor of Anatomic Pathology at the University of Tennessee College of Veterinary Medicine. Conference discussion began with a discussion of the bony features present in the examined section, followed by a discussion of basic definitional terms. Mature bone is divided into compact (also called cortical) and cancellous (also called spongy) varieties. The collagen in compact bone is typically oriented into a strong parallel, lamellar arrangement that is organized into osteons, and this dense, compact bone is typically present on the peripheral or exterior portion of the bone. The collagen in cancellous bone is less dense than compact bone, with collagen organized into trabeculae which create cavities that may contain bone marrow. Bone can also be categorized as lamellar or woven, with the former being characterized by mature, organized collagen and the later characterized by more

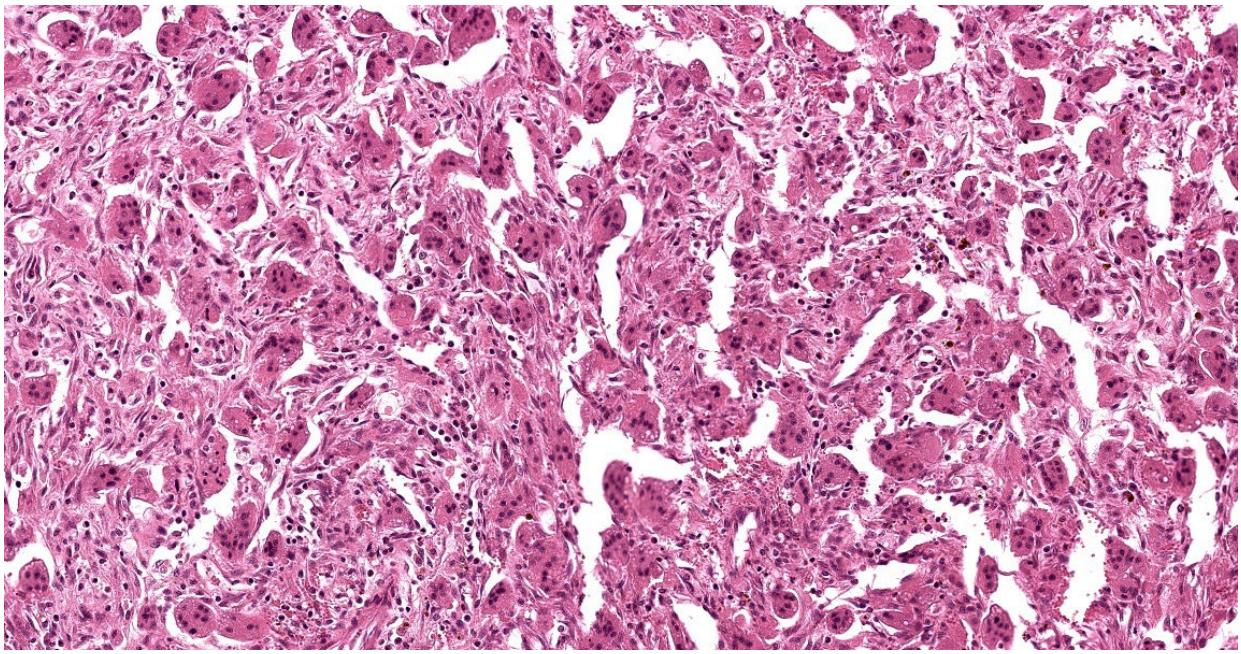

Figure 1-6. Mandible, goat. High magnification of the neoplastic cells composing the mass. Multinucleated cells are common. (HE, 147X)

immature, haphazardly arranged collagen fibers. Woven bone represent early osteogenesis and will typically be remodeled and replaced by lamellar bone as it matures. Woven bone can be easily distinguished from lamellar bone by the use of polarized light, which highlights the degree of collagen organization present in the tissue.

Dr. Craig discussed other entities characterized by giant cells, including giant cell tumor of soft parts, giant cell osteosarcoma, peripheral giant cell granuloma, and ethmoid hematomas. Participants discussed the differences between these entities and how the line between reactive and neoplastic seems particularly porous with these entities. Participants noted that "central giant cell granuloma" appears to be a human entity that is rarely diagnosed in veterinary medicine. Though typically occurring in the long bones and digits, participants favored a diagnosis of giant cell tumor of bone, a well-described veterinary entity with a histologic appearance identical to the examined tissue.

References:

1. Chandna P, Srivastava N, Bansal V, Wadhwan V, Dubey P. Peripheral and central giant cell lesions in children: institutional experience at Subharti Dental College and Hospital. *Indian J Med Paediatr Oncol.* 2017;38(4):440.
2. De Bruijn ND, Kirpensteijn J, Neyens IJS, Van den Brand JMA, Van den Ingh TSGAM. A clinicopathological study of 52 feline epulides. *Vet Pathol*. 2007; 44(2):161-169.
3. Desoutter AV, Goldschmidt MH, Sánchez MD. Clinical and histologic features of 26 canine peripheral giant cell granulomas (formerly giant cell epulis). *Vet Pathol*. 2012;49(6):1018-1023.
4. Dixon J, Weller R, Jeckel S, Pool R, Mcsloy A. Imaging diagnosis—the computed tomographic appearance of a giant

cell tumor affecting the mandible in a pygmy goat. *Vet Radiol Ultrasound*. 2016; 57(5):1-3.
5. Gandara-Rey JM, Pacheco JMC, Gandara-Vila P, et al. Peripheral giant-cell granuloma. Review of 13 cases. *Med Oral.* 2002;7(4):254-259.
6. Hiscox LA, Dumais Y. Peripheral Giant Cell Granuloma in a Dog. *J Vet Dent.* 2015;32(2):103-110.
7. Kruse-Lösler B, Diallo R, Gaertner C, Mischke KL, Joos U, Kleinheinz J. Central giant cell granuloma of the jaws: a clinical, radiologic, and histopathologic study of 26 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2006;101(3):346-354.
8. Jané-Salas E, Albuquerque R, Font-Muñoz A, González-Navarro B, Estrugo Devesa A, López-López J. Pyogenic granuloma/peripheral giant-cell granuloma associated with implants. *Int J Dent.* 2015; 2015:839032.
9. Lester SR, Cordell KG, Rosebush MS, Palaiologou AA, Maney P. Peripheral giant cell granulomas: a series of 279 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2014;118(4):475-482.
10. Motamedi MHK, Eshghyar N, Jafari SM, et al. Peripheral and central giant cell granulomas of the jaws: a demographic study. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2007;103(6);e39-e43.
11. Uzal FA, Plattner BL, Hostetter JM. Alimentary System. In: Maxie MG, ed. *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*. 6th ed. Vol 2. Elsevier; 2016:20-22.
12. Papdaki ME, Lietman SA, Levine MA, Olsen BR, Kaban LB, Reichenberger EJ. Cherubism: best clinical practice. *Orphanet J Rare Dis*. 2012;24(Suppl 1):S6.

Figure 2-1. Vertebral column, chicken. At T4-T5, there is an abscess, pathologic fracture of the vertebral body, and compression of the spinal cord. (*Photo courtesy of:* Department of Veterinary Biosciences and Australian Pacific Centre for Animal Health, Melbourne Veterinary School, The University of Melbourne, Werribee, Victoria, Australia; and Inghams Enterprises, Victoria, Australia, unimelb.edu.au)

CASE II:

Signalment:
40-day-old male Cobb broilers (*Gallus gallus domesticus*)

History:
Two male 40-day-old Cobb broilers from a commercial farm in Victoria were submitted for necropsy and diagnostic work up following euthanasia by cervical dislocation. The farm was culling 200 birds per shed (approximately 0.5% of birds) at the time. The submitting veterinarian reported that the birds have normal mentation but have paresis or paralysis and a characteristic posture, sitting back on their hocks with legs extended in front of them and wing walking. Post mortem examination of one bird by the submitting veterinarian showed a small bursa and femoral head necrosis.

Gross Pathology:
Both birds examined were well-preserved and in good body condition. The free thoracic vertebra was expanded and effaced by a yellow-

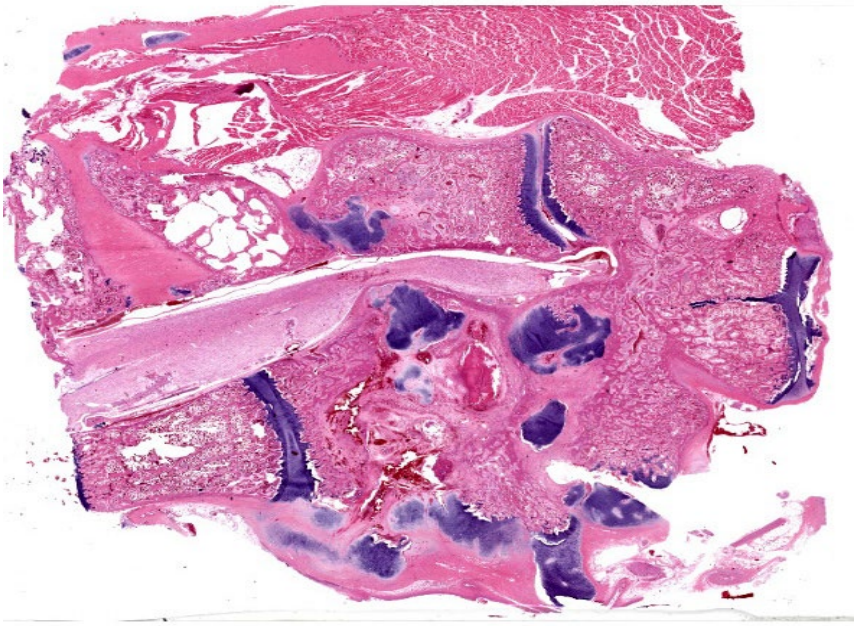

Figure 2-2. T4-T5 vertebrae, chicken. There is fracture of the vertebral body with a focal heterophilic granuloma, compression of the spinal cord, and callus formation with abundant production of cartilaginous matrix. (HE, 5X)

tan multinodular mass that appeared to be inflammatory, associated with a presumably pathologic fracture, and to focally and severely compress the spinal cord. The bisected T4-T5 vertebral sections of both subjects revealed focal red discolouration of the hypaxial muscles surrounding the cord compression focus. The left femoral head was diffusely, markedly red on the articular surface and appeared enlarged compared to the right in both birds. There was some soiling (brown, soft material) of the vent of one bird. The bursa and other organs, including other vertebrae examined, showed no noteworthy changes grossly.

Laboratory Results:

Aerobic culture (vertebral abscess swabs) yielded a lightly contaminated growth, with *Enterococcus cecorum* isolated as the predominant organism.

Microscopic Description:

Histologically, the femur, bursa, and other organs apart from the free thoracic vertebra (FTV) showed no noteworthy changes. In both birds, covering over 70% of the sagittal plane examined, the architecture of the vertebral bodies of T4/T5 was largely obliterated and replaced by extensive multinodular callus formation. The spinal cord was severely compressed at this level by the callus. There was mild to moderate Wallerian degeneration characterised by vacuolation of the adjacent white matter, with spheroids, degenerate macrophages, or axonal debris noted in some vacuoles, these changes interpreted as confirming that the compression was real, as opposed to a plane of section artifact. Within the vertebra, there was extensive necrosis, osteolysis, oedema, fibrin deposition, haemorrhage and moderate infiltration by heterophils, histiocytes, lymphocytes, and plasma cells. Multi

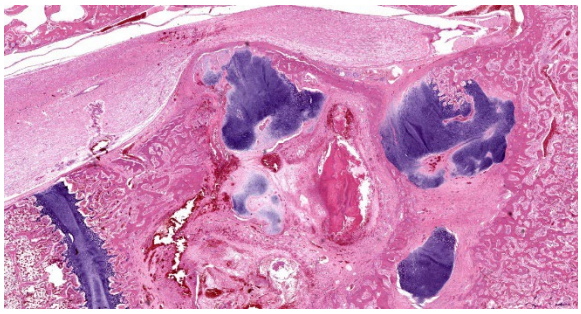

Figure 2-3. T4-T5 vertebrae, chicken. Higher magnification of the heterophilic granuloma and callus causing spinal cord compression. (HE, 13X)

focally within these areas of necrosis and remodelling there were large numbers of small monomorphic bacterial aggregates (mainly cocci). On Gram stained sections, these were shown to be gram positive cocci.

Contributor's Morphologic Diagnosis:
T4/T5 vertebrae: Spondylitis, severe, heterophilic, lymphoplasmacytic, haemorrhagic, necrotising with extensive remodelling, pathologic fracture, callus formation and focal spinal cord compression.

Contributor's Comment:
The colloquial term "kinky back" is occasionally used in practice to refer to Enterococcal spondylitis of the T4/T5 vertebrae. *Enterococcus cecorum* is a gram-positive enteric commensal of poultry; however, strains of *E. cecorum* causing outbreaks have significantly smaller genomes than commensal *E. cecorum*.[1] Pathogenic *E. cecorum* has also been reported to cause disease in Pekin ducklings and pigeons. The posture of the broilers (sitting back on their hocks) is characteristic, although not pathognomonic of this condition. Wing walking is used for locomotion, and this also limits their access to food. An interesting feature of this condition is the characteristic lesion localisation at the free thoracic vertebra (FTV). The FTV has greater weight-bearing articulations compared to the adjacent notarium and synsacrum, potentially predisposing it to infection with pathogenic *E. cecorum*.

Another condition that is also referred to as "kinky back" is spondylolisthesis caused by subluxation of the fourth thoracic vertebra (T4). Ventral displacement of the cranial end of T4 also results in compression of the spinal cord via narrowing of the vertebral canal (dorsal projection of its posterior extremity). The aetiology of spondylolisthesis is primarily genetic, as opposed to bacterial as is the case for enterococcal spondylitis, but the occurrence is influenced by increased growth rate.

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Melbourne Veterinary School
The University of Melbourne
Werribee, Victoria, Australia
unimelb.edu.au

JPC Diagnosis:
Vertebrae: Spondylitis, necrotizing, focally extensive, severe, with pathologic fracture, callus, and focal spinal cord compression.

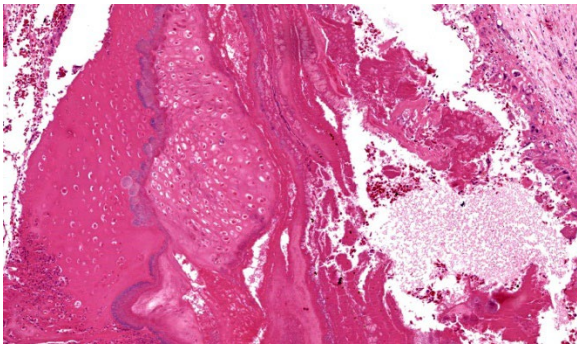

Figure 2-4. T4-T5 vertebrae, chicken. High magnification of the heterophilic granuloma with incorporated necrotic bone. (HE, 13X)

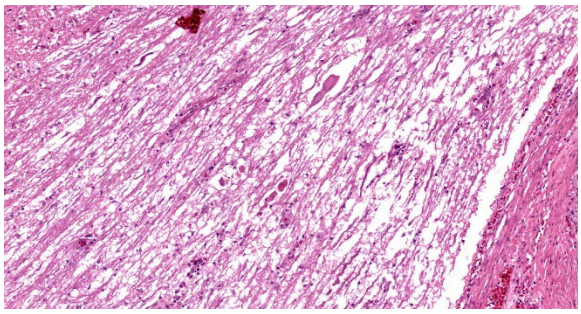

Figure 2-5. Thoracic spinal cord, chicken. There is Wallerian degeneration of the spinal cord at the area of compression with edema, dilation of myelin sheaths, and spheroid formation. (HE, 189X)

JPC Comment:

This case provides an excellent example of a classic entity of poultry. As the contributor notes, one of the curiosities of Enterococcal spondylitis (ES) is its tropism for the free thoracic vertebra (FTV). Cranial to the FTV, the thoracic vertebrae are fused into the notarium via synchondrosis rather than with synovial articulations and intervertebral discs, as in mammals.[1] Caudal to the FTV, the caudal thoracic vertebrae, lumbosacral vertebrae, and the pelvic bones are similary fused into the synsacrum, leaving the FTV as the only vertebra in the thoracolumbar column to have weight bearing articulations.[1] This anatomic oddity places substantial mechanical stress on the FTV as it transfers body weight to the hips and hind limb, perhaps predisposing the FTV to injury and to subsequent infection with pathogenic *Enterococcus cecorum*.[1]

By the time clinical signs are evident, typically in weeks 4-6 of life, spinal lesions are already well developed, with histologic evidence of chronic infection.[1] A recent study evaluated lesion development in ES during the first four weeks of life, when affected chickens are incubating subclinical disease. The study found that the first step in the development of ES is the colonization of the gut by pathogenic *E. cecorum* species within the first week of life. This is in contrast to commensal *E. cecorum*, which arrives in the chicken gut around 3 weeks of age. The authors speculate that the ability to colonize the gut early in life may be a key virulence event, conveying a competitive advantage that allows pathogenic bacteria to disseminate throughout a flock.[1]

A second likely step in ES pathogenesis is the development of osteochondrosis dissecans (OCD) lesions in the FTV.[1] OCD lesions progress through a stereotypical sequence, thought to be initiated and driven by vascular disturbances or increased type II collagen production.[2] The earliest changes observable in the cartilage consist of a poorly defined focus of eosinophilia and hypocellularity in the articular cartilage, termed osteochondrosis latens, which may extend to the subchondral bone.[1,2] These areas may remain stable, or may progress to osteochondrosis manifesta, characterized by areas of cartilage retention in the ossification zone.[1] Finally, fully-fledged OCD lesions are characterized by clefts in the hyaline cartilage which may communicate with the joint space or extend into subchondral bone.[1,2]

Large cartilaginous clefts are the hallmark lesion of OCD and are readily identifiable in affected birds as early as 1 week of age; these clefts are variably filled with fibrin, erythrocytes, and, in some birds, bacterial cocci consistent with *E. cecorum*.[1] These lesions progress over the next two weeks with an influx of heterophilic and histiocytic inflammation targeting these cocci-filled cartilaginous clefts.[1] Continued progression leads to the bone remodeling and spinal cord compression that comprise the stereotypical ES lesion.[1]

It remains unclear why cartilage clefting predisposes chickens to ES lesions. One theory is that hemorrhage into the cartilage clefts introduces bacteremic, pathogenic *E. cecorum* to the site of injury and, once there, the devitalized cartilage provides a favorable niche for bacterial persistence and proliferation. Whatever the reason, the unique anatomic features of the weight-bearing FTV, which articulates through epiphyseal cartilage without the benefit of joint capsules or intervertebral discs, makes it uniquely susceptible to trauma, and the FTV is the only location within the vertebral column where OCD lesions and subsequent *E. cecorum* colonization occur.[1]

Dr. Craig discussed the alternating layers of bacteria and cartilage within the lesion. These layers provide histologic support for the tidy pathogenic narrative discussed above. Without engaging in excessive flights of fancy, it is easy to imagine the successive rounds of cartilage clefting and bacterial colonization that result in this spectacular ES lesion. Dr. Craig also noted several basophilic, circular areas within the tissue that represent residual mineral left over from the decalcification process. These artifacts can be misinterpreted as mast cells, macrophages, or other histologic features, and can be avoided by copious rinsing of tissue after decalcification and prior to further processing.

Discussion of the morphologic diagnosis focused initially on whether to include the various inflammatory cells present in the lesion. Conference participants felt that the chronic nature of the lesion, evidenced by callous formation, implied the existence of a chronic inflammatory infiltrate and made the inclusion of this histologic feature superfluous. Partipants also decided to omit the bacterial cocci which, while confirmed with Gram stain, were not convincingly evident to all participants based on H&E evaluation alone.

References:

1. Borst LB, Suyemoto MM, Sarsour AH, et al. Pathogenesis of enterococcal spondylitis caused by *Enterococcus cecorum* in broiler chickens. *Vet Pathol*. 2017;54:61-73.
2. Olstad K, Ekman S, Carlson CS. An update on the pathogenesis of osteochondrosis. *Vet Pathol*. 2015;52(5):785-802.

CASE III:

Signalment:
4-year-old, female spayed Standard poodle dog (*Canis familiaris*)

History:
A pilomatrixoma was excised from this animal's tail base two years prior to presentation for non-weight bearing lameness on the right pelvic limb. Polyostotic aggressive bone lesions were seen on survey radiography. Staging identified pulmonary nodules.

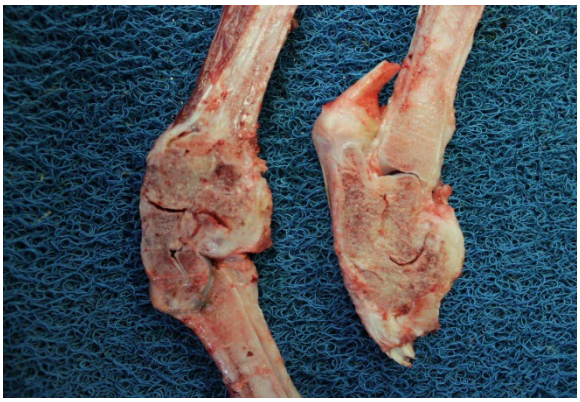

Figure 3-1. Tibia and tarsus, dog. A hard mass surrounds the hock joint and involves the tarsal and metatarsal bones. (*Photo courtesy of*: the Department of Pathology, University of Guelph).

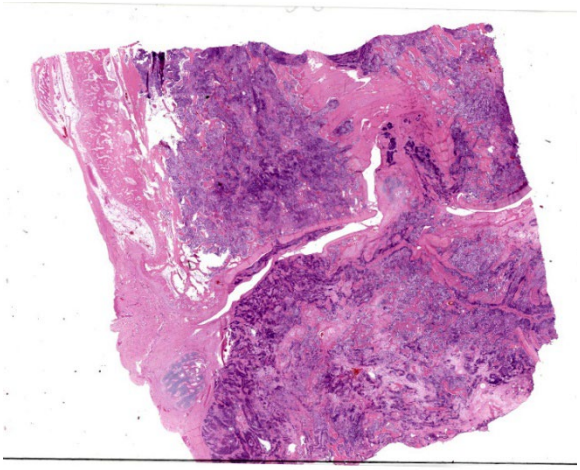

Figure 3-2. Long bone, dog. The cortical and medullary architecture is effaced by a large infiltrative mass. (HE, 6X)

Gross Pathology:
The right hock is circumferentially expanded by a hard, round mass. There is a mass involving the tarsal bones and the metatarsals. There is marked periosteal new bone formation of the distal tibia. There are multiple 1-5 cm nodules throughout the lungs.

Microscopic Description:
This sample has remnants of normal bone and bony trabeculae of the subchondral/epiphyseal regions. There is a small amount of articular cartilage, some joint space and joint capsule, and opposing bone across and around the joint space. Much of the cortical and trabecular bone is missing and the intertrabecular spaces are filled with sheets of hyperchromatic cells with focal areas of keratin formation. There is some periosteal new bone formation at the edge of the cortical bone and some endosteal new bone formation, but about 90% of this sample is neoplastic tissue. Neoplastic cells form nodules, clusters, and streams of cells that completely fill the intertrabecular spaces. There are some bands of fibrous tissue throughout the lesion. In the centre of nodules and clusters are small hyperchromatic cells similar to those on the periphery and in some, the central cells have more cytoplasm. In many, the cytoplasm is vacuolated. In occasional focal areas there is keratinization with dense keratin and the ghostlike nuclear outline of matricial keratinization. About 10% of this mass is necrotic.

Contributor's Morphologic Diagnoses:
Metastatic pilomatrixoma to bone with extensive bony lysis and periosteal and endosteal new bone formation.

Contributor's Comment:
The appearance of the cells within the bone and similar appearing cells in the lung (not provided) with keratinization of the matricial type is typical of metastasis of pilomatrixoma. It is rare for pilomatrixoma to metastasize, but when they do, previous reports indicate metastasis to the bone is common.

Contributing Institution:
Department of Pathobiology
Ontario Veterinary College
University of Guelph
Guelph, Ontario,Canada

JPC Diagnosis:
Bone: Metastatic pilomatricoma.

JPC Comment:
Pilomatricoma (also known as pilomatrixoma) is an adnexal neoplasm that arises from the germinative cells of the follicular matrix, or hair bulb, and is reported mainly in dogs and humans.[1,8] Pilomatricomas are diagnosed most commonly in 4-8 year-old dogs, and Kerry Blue Terriers, Soft Coated Wheaten Terriers, Standard Poodles, and other breeds with continuously growing hair coats are overrepresented in the patient pool, likely because the high number of anagen hair follicles,

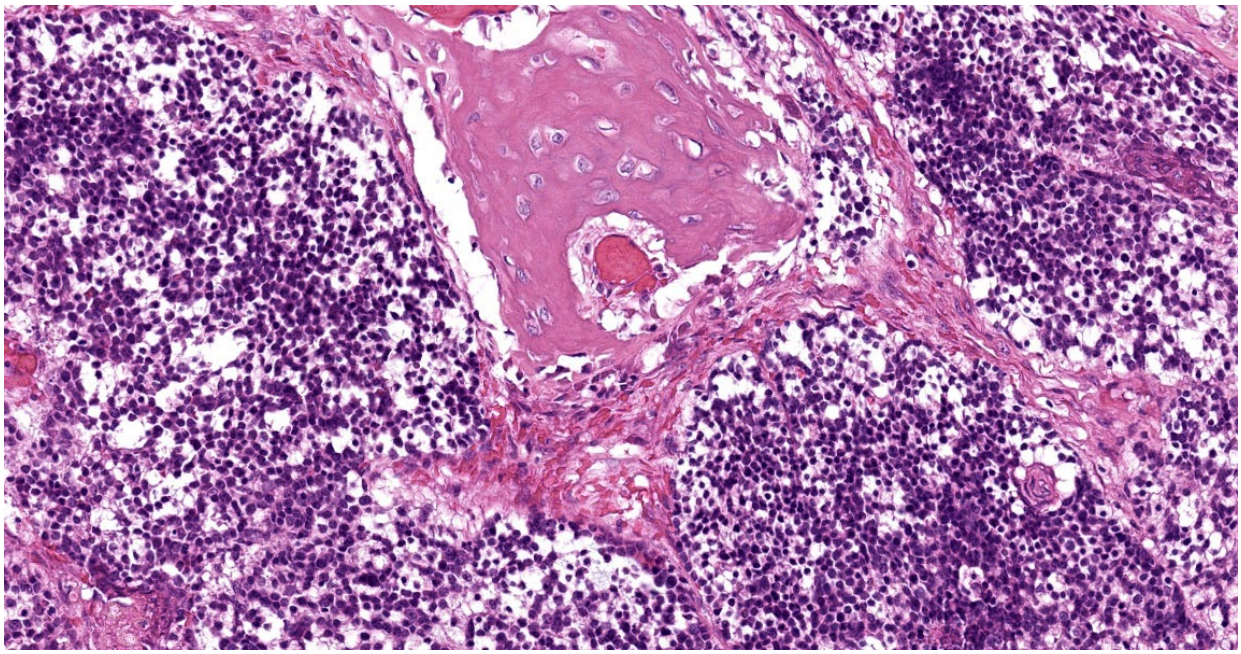

Figure 3-3. Long bone, dog. The neoplasm is composed of small polygonal densely-packed epithelial cells arranged in nests and packets. Remodeling periosteal bone is at center, top. (HE, 177X)

and their attendant replicating cells, provide fertile soil for neoplastic transformation.[1]

Consistent with their follicular origin, pilomatricomas typically present as intradermal or subcutaneous masses composed of one or more lobules separated by collagenous stroma.[3] The lobules contain a peripheral zone of basophilic cells with hyperchromatic nuclei, a high N:C ratio, and a moderate to high number of mitotic figures.[3] The neoplastic cells exhibit an abrupt transition to a central zone of ghost cells which often contain significant accumulations of melanin.[3]

As the contributor notes, most pilomatricomas exhibit benign, non-metastatic biologic behavior and excision with wide surgical margins is typically curative.[3] Malignant pilomatricoma is typically differentiated from its bengin counterpart by being poorly circumscribed, less differentiated, anaplastic, infiltrative, rapidly or erratically growing, and, definitially, metastatic.[1,3] Metastatic pilomatricoma has been reported in various organs, including lymph nodes, lungs, bone, and skin; metastasis to the liver and spleen is less common.[1,8] Despite the variety of reported metastatic sites, malignant pilomatricoma seems predisposed to metastasize to bone, with metastasis reported in vertebrae, ribs, the mandible, maxilla, and femur.[1]

The primary differential for primary or metastatic malignant pilomatricoma is malignant trichoepithelioma, a follicular neoplasm with differentiation to all three segments of the hair follicle.[3] Differentiating between these two neoplasms can be difficult, but malignant trichoepitheliomas have tricohyaline granules and prominent inner and outer root sheath differentiation, along with smaller epithelial aggregates, fewer matrical cells, and fewer ghost cells.[1,3]

The moderator began discussion by noting the palisading layer of cells around the periphery of the neoplastic trabeculae, the first clue that

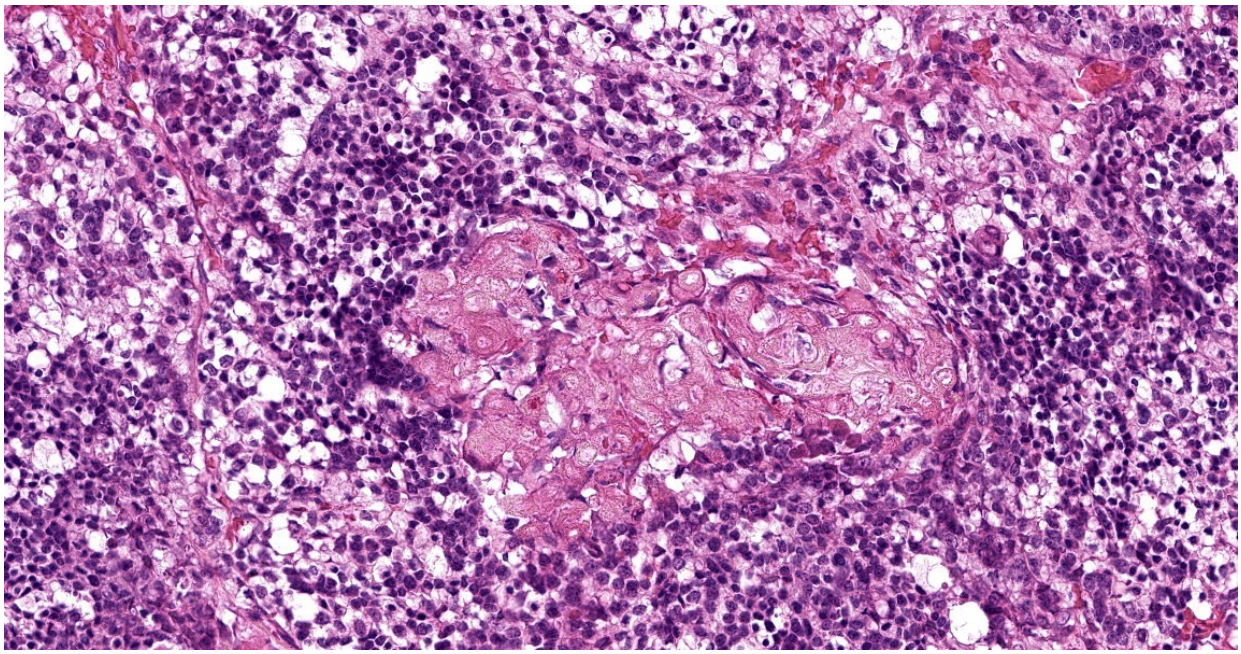

Figure 3-4. Long bone, dog. There are numerous foci of abrupt keratinization of neoplastic cells. (HE, 314X)

this neoplasm is of epithelial origin. Dr. Craig also noted that the islands of ghost cells can be easily mistaken for necrotic bone with empty lacunae without careful examination. Dr. Craig, a self-described breed predisposition enthusiast, noted that Bassett Hounds are predisposed to pilomatricomas generally and since pilomatricomas often metastasize to bone, metastatic pilomatricoma should be on the differential list for lameness in this breed. As an additional breed-related curiosity, Dr. Craig noted that large breed black dogs, such as the Standard Poodle, Giant Schnauzer, Bouvier des Flanders, and others, unrelated except for size and color, are predisposed to multiple digital squamous cell carcinomas.

The moderator lead a more general discussion of carcinomas within bone, noting that metastatic carcinoma is more common than primary bone tumors in many species. In dogs, metastasis to bone is most frequent in the ribs, vertebrae, and proximal long bones. Dr. Craig noted that most textbooks state that metastasis of carcinomas to bone is uncommon in sites distal to the elbow or stifle; however, there are many examples, including this case, in which metastatic carcinoma is found in more distally, making location an unreliable diagnostic criterion for metastatic carcinoma.

References:

1. Carroll EE, Fossey SL, Mangus LM, et al. Malignant pilomatricoma in 3 dogs. *Vet Pathol*. 2010;47(5):937-43.
2. da Silva EO, Green KT, Wasques DG, Chaves RO, dos Reis AC, Bracarense AP. Malignant pilomatricoma in a dog. *J Comp Pathol*. 2012;147(2-3):214-217.
3. Goldschmidt MH, Minday JS, Scruggs JL, Klopfleisch R, Kiupel M. *Surgical Pathology of Tumors of Domestic Animals*. Vol 1: Epithelial Tumors of Skin. The Davis-Thompson Foundation; 3rd ed:112-114.
4. Huzella L, Ide A, Steinbach TJ, Blanchard TW, Lipscomb TP, Schulman FY. Osteosarcoma in malignant pilomatricoma. *Vet Pathol* 2005;42:700.

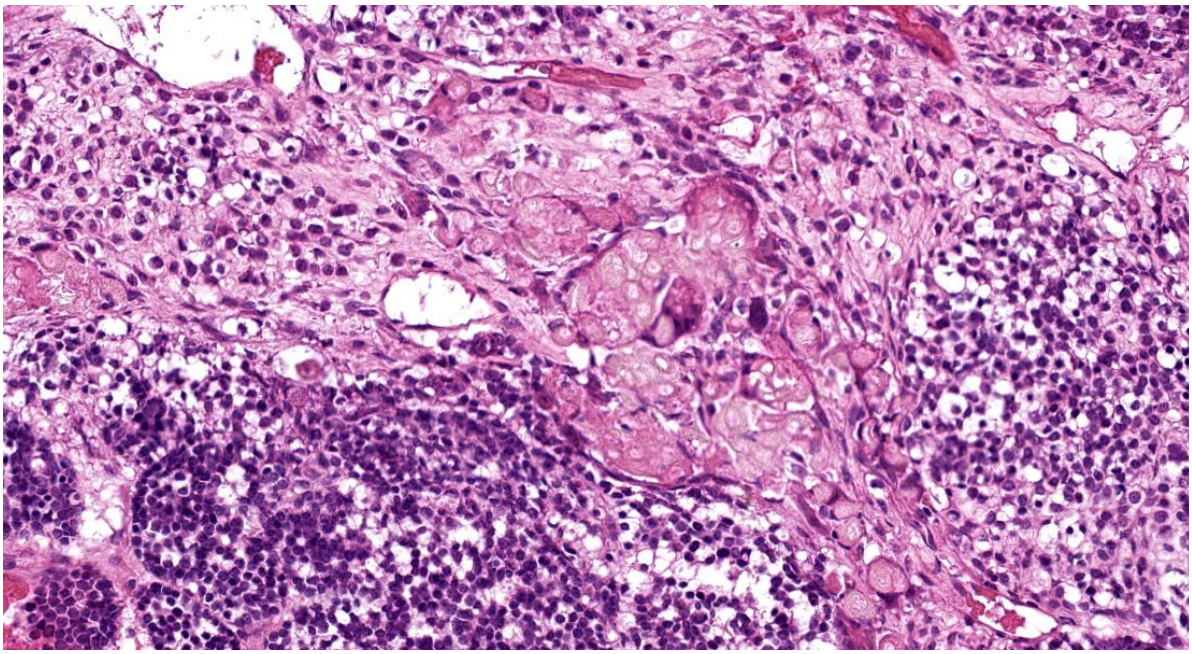

Figure 3-5. Long bone, dog. In some foci, abrupt keratinization has resulted in the formation of "ghost cells" which are characteristic of follicular tumors, particular pilomatricoma. (HE, 314X)

5. Jackson K, Boger L, Goldschmidt M, Walton RM. Malignant pilomatricoma in a soft-coated Wheaten Terrier. *Vet Clin Pathol.* 2010;39(2):236-40.
6. Johnson RP, Johnson JA, Groom SC, Burgess L. Malignant pilomatrixoma in an old english sheepdog. *Can Vet J.* 1983;24: 392-394.
7. Martano M, Navas L, Meomartino L, et al. Malignant pilomatricoma with multiple bone metastases in a dog: histological and immunohistochemical study. *Exp Ther Med*. 2013;5(4):1005-1008.
8. Treggiari E, Elliott JW. Malignant pilomatricoma in a dog with local and distant metastases treated with chemotherapy and bisphosphonates. *Open Vet J.* 2017; 7(3):208-213.

CASE IV:

Signalment:
3-year-old, male intact budgerigar *(Melopsittacus undulatus)*

History:
This animal was a member of a zoological collection and was found dead in its enclosure.

Gross Pathology:
This blue, 39.3g male budgerigar had a dark blue cere. Both testes were enlarged (left was bilobed and 8x5x5mm, right was spherical and 5x5x5mm in diameter).

Microscopic Description:
Both testes (slide not provided) contained a neoplasm composed of polygonal cells in packets separated by a dense fibrous stroma. Neoplastic cells had distinct borders, eosinophilic cytoplasm, and round nuclei. Foci of a similar neoplastic population were within the marrow of both femurs. Both femurs and humeri had basophilic, non-birefringent bone lining the medullary trabeculae (medullary

Figure 4-1. Presentation, parakeet. This male parakeet had a dark blue cere. (*Photo courtesy of:* University of Tennessee College of Veterinary Medicine, Department of Biomedical and Diagnostic Sciences, 2407 River Drive, Room A201, Knoxville, TN 37996, https://vetmed.tennessee.edu/academics/biomedical-and-diagnostic-sciences/)

bone) that was most pronounced near the metastatic foci.

Contributor's Morphologic Diagnosis:
Femur: Metastatic Sertoli cell tumor with associated medullary bone.

Contributor's Comment:
Medullary bone (also known as laying bone) is formed and removed along the endosteal surfaces of bones in female birds during the egg-laying cycle as a source of calcium for eggshells. In females, it typically spares the pneumatic bones, mostly forming in the hematopoietic bones such as the femur and tibiotarsus, but this varies with species.

This femur is from one of 7 male budgerigars in a publication that described medullary bone as a feature of paraneoplastic feminization. The medullary bone deposition was diffuse in 4 cases and multifocal in 3 (including this one) and affected both pneumatic (humeri) and hematopoietic (femurs) bones.[2] This was the only case in which bony metastases were detected. Interestingly, the medullary bone in this case is most pronounced near the metastatic foci.

The testicular tumors associated with medullary bone included Sertoli (sustentacular) cell tumors, seminomas, and one mixed (Sertoli-interstitial cell) tumor.[2] Although estrogen production is characteristic of Sertoli cells tumors, estrogen production and feminization have been reported in humans and dogs with seminomas.[1,3]

Female budgerigars normally have a bright pink cere, while males have a light blue cere. Cere color change is another feature of paraneoplastic feminization reported in budgerigars.[4] In the published study of 7 budgerigars with testicular tumors and medullary bone, 4 had a blue-brown or red-brown cere, 2 had a light blue cere, and one (this bird, case 3 in reference 2) had a dark blue cere.[2]

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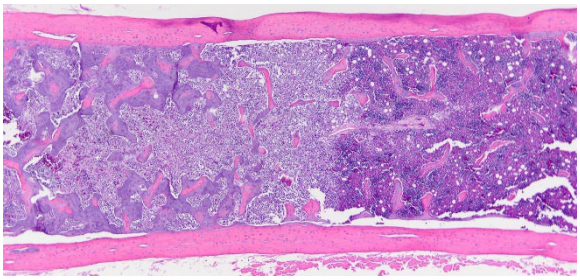

Figure 4-2. Femur, parakeet. The medullary cavity has a focus of metastatic neoplasia. (HE, 40X)(*Photo courtesy of*: University of Tennessee College of Veterinary Medicine, Department of Biomedical and Diagnostic Sciences, 2407 River Drive, Room A201, Knoxville, TN 37996)

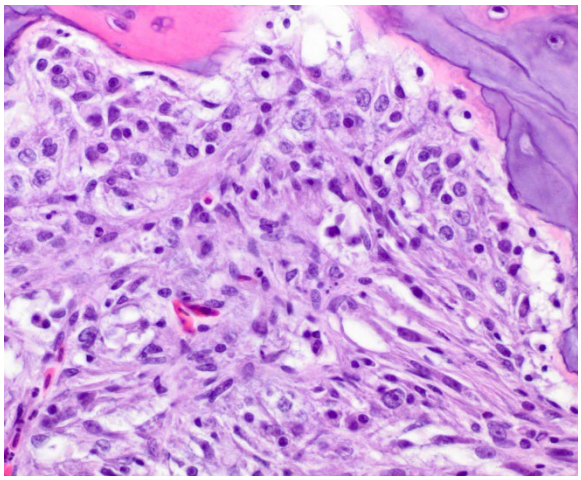

Figure 4-3. Femur, parakeet. High magnification of neoplastic cells. (HE 400X)(*Photo courtesy of*: University of Tennessee College of Veterinary Medicine, Department of Biomedical and Diagnostic Sciences, 2407 River Drive, Room A201, Knoxville, TN 37996)

JPC Diagnosis:
Long bone: Metastatic sustentacular cell tumor with associated medullary bone.

JPC Comment:
This fascinating case provides an excellent example of medullary bone, a new concept for many conference participants this week. As noted by the contributor, medullary bone is normally produced in the hematopoietic bones of female birds to serve as calcium stores for the arduous task of mineralizing eggs. This sex-specific tissue is produced by female birds from approximately 10 days pre-ovulation until the completely mineralized egg is laid.[2] Medullary bone can be distinguished from woven bone by its increased basophilia, due to an increased proteoglycan content compared to woven bone, and by the absence of birefringence under polarized light.[2]

The formation of medullary bone occurs simultaneously with the maturation of ovarian follicles, and is believed to be due to incompletely understood interactions among the hypothalamus, pituitary gland, and ovaries.[2] The ovum produces estrogens upon the binding of luteinizing hormone produced by the pituitary gland, and these estrogens bind estrogen receptors on osteoblasts, leading to the deposition of type I collagen on the endosteal surfaces of hematopoietic bones of female birds.[2] Once the egg is ovulated and reaches the shell gland, mineralization-induced hypocalcemia induces parathyroid hormone secretion, which in turn stimulates osteoclasts to resorb medullary bone, releasing calcium stores into the bloodstream for use in egg mineralization.[2]

The contributor provides an excellent overview of the concept of paraneoplastic feminization, defined as "the acquisition of feminine characteristics as an indirect consequence of a neoplasm, usually due to production of chemical signalling molecules such as hormones."[2]

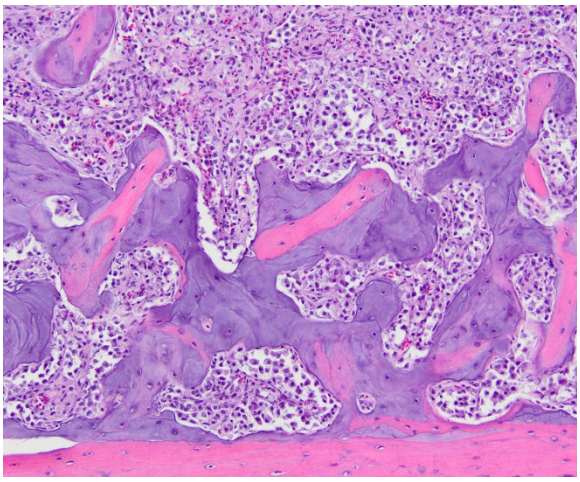

Figure 4-4. Femur, parakeet. The bone adjacent to the neoplasm has a densely basophilic matrix covering the endosteum, which is called "medullary" or "laying" bone. (*Photo courtesy of*: University of Tennessee College of Veterinary Medicine, Department of Biomedical and Diagnostic Sciences, 2407 River Drive, Room A201, Knoxville, TN 37996)

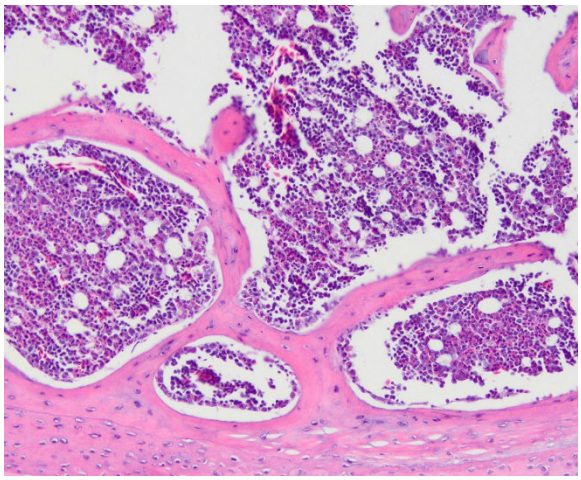

Figure 4-5. Femur, parakeet. For comparison, in areas of marrow devoid of neoplastic cells, the bone is of normal morphology. (*Photo courtesy of:* University of Tennessee College of Veterinary Medicine, Department of Biomedical and Diagnostic Sciences, 2407 River Drive, Room A201, Knoxville, TN 37996)

In veterinary medicine, this condition is well-described in male dogs with sustentacular (Sertoli) cell tumors, in which estrogen production by neoplastic cells produces female behavior and other characteristic changes such as gynecomastia, alopecia, prostatic squamous metaplasia, and myelosuppression.[2] Removal of the neoplastic tissue typical results in normalization of serum estrogen and reversion to more gender-stereotypic behavior and physiology. In male budgerigars with testicular neoplasia, paraneoplastic feminization is typically described as involving medullary bone formation, cere color change, widening of the pelvic inlet, and protrusion of the cloaca.[2] The production of medullary bone can be diagnostically useful, as the resulting increase in bone density can be identified radiographically and can serve as an early indication of testicular neoplasia.[2]

Conference discussion focused on the histologic appearance of medullary bone, including the basophilia and lack of birefringence, as noted above. Conference participants also examined Masson and Movat pentachrome stains, in which the medullary bone stained blue and green, respectively. The moderator noted that medullary bone in male budgerigars can be present with all three testicular tumors though not all produce the estrogen throught responsible for the formation of medullary bone. This curiosity highlights the fact that the physiologic basis for medullary bone deposition remains incompletely understood and is likely multifactorial.

References:

1. Duparc C, Boissiere-Veverka G, Lefebvre H, et al. An oestrogen-producing seminoma responsible for gynaecomastia. *Horm Metab Res*. 2003;35(5):324-329.
2. Hoggard NK, Craig LE. Medullary bone in male budgerigars (*Melopsittacus undulatus*) with testicular neoplasms. *Vet Pathol.* 2022;59(2):333-339.
3. Kim O, Kim KS. Seminoma with hyperesterogenemia in a Yorkshire terrier. *J Vet Med Sci*. 2005;67(1):121-123.
4. Mans C, Pilny A. Use of GnRH-agonists for medical management of reproductive disorders in birds. *Vet Clin North Am Exot Anim Pract*. 2014;17(1):23–33.