WEDNESDAY SLIDE CONFERENCE 2014-2015

Conference 22

22 April 2015

Guest Moderator:
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CASE I: 459-12 (JPC 4017816).

Signalment: Tissue from a domestic duck, *Anas platyrhynchos domesticus*.

History: One duck was submitted for being lethargic with emaciation and ataxia.

Gross Pathologic Findings: No gross lesions were seen other than slight emaciation.

Laboratory Results (clinical pathology, microbiology, PCR, ELISA, etc.)**:** 1+ *Pasteurella multocida* and 1+ *E. coli* were isolated from the lung and liver swabs and no bacterial growth was obtained from the heart swab.

Histopathologic Description: The heart has multifocal small areas of necrosis and moderate multifocal mixed inflammation with heterophils, lymphocytes, and some histiocytes. Bacterial colonies and emboli are throughout the

1-1. Heart, duck: At subgross there is a cellular infiltration throughout the myocardium. (HE 3X)
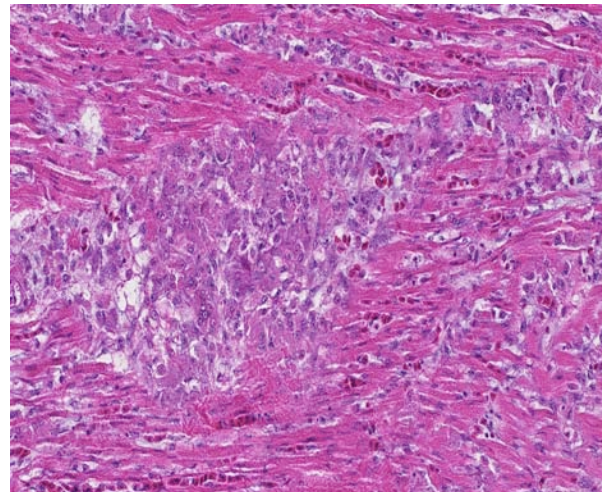
1-2. Heart, duck: Large areas of necrotic cardiac muscle are infiltrated and replaced by numerous macrophages admixed with fewer multinucleated foreign-body type macrophages. (HE 224X)
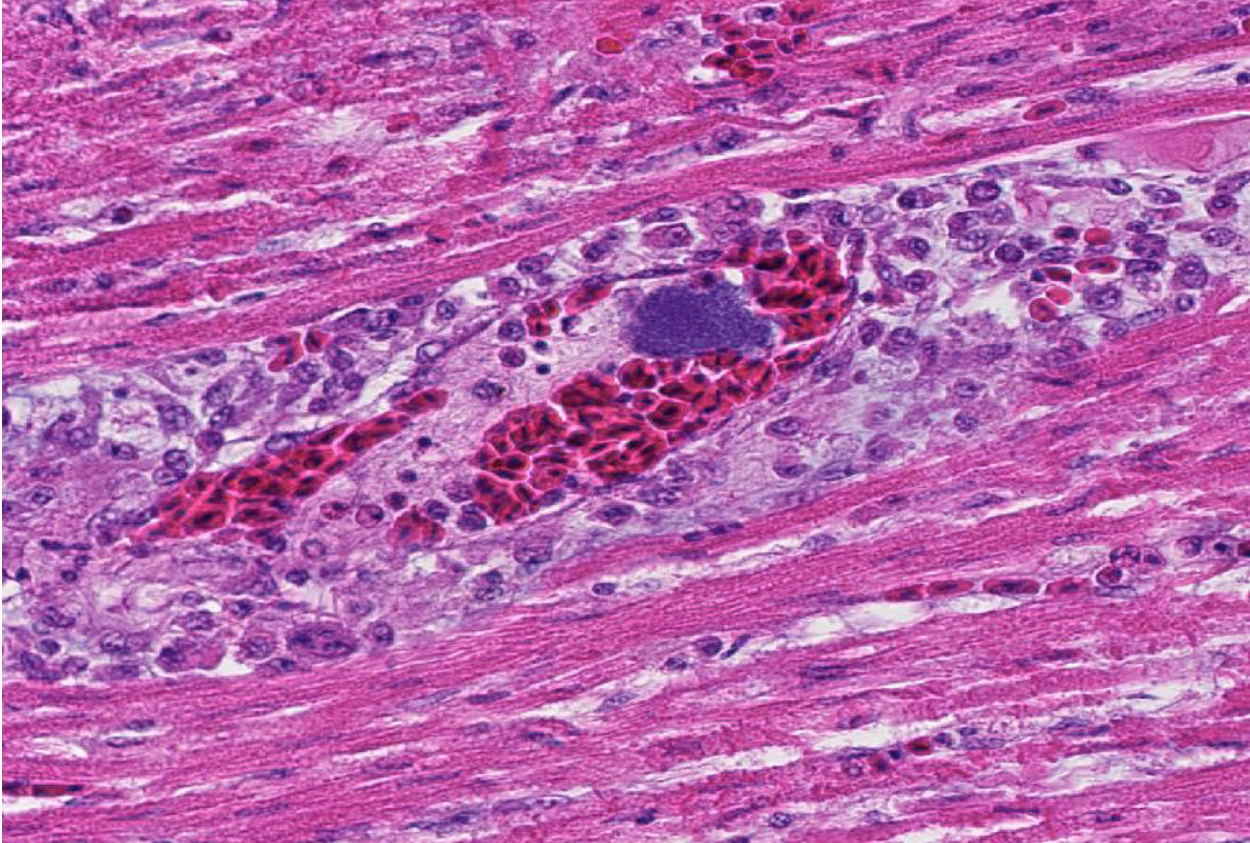
1-3. Heart, duck: Bacterial emboli are present within numerous myocardial vessels, and there is often marked histiocytic perivascular inflammation. (HE 224X)

myocardium. Mixed leukocytes with fibrin and a few multinucleated giant cells are on the epicardium. The lung section was congested and had a bacterial embolus but no inflammation and the liver was normal other than sinusoidal histiocytosis. No lesions were seen in the brain, intestine, and kidney sections (only heart from this case was submitted.)

Contributor's Morphologic Diagnosis: Multifocally necrotizing and subacute myocarditis.

Contributor's Comment: This is fowl cholera septicemia (*Pasteurella multocida*). *E. coli* was not thought to be significant and *P. multocida* is always considered to be significant from poultry. Chickens usually have a chronic disease with pasteurellosis, with infection in the combs and wattles. The bacteria can often also be isolated from internal organs. Turkeys and ducks are more likely to have an acute or peracute infection, often with many acute deaths.[3]

JPC Diagnosis: Heart: Myocarditis, necrotizing and histiocytic, multifocal to coalescing, severe, with vasculitis, thrombosis, fibrinous epicarditis, and intra- and extracellular bacterial colonies.

Conference Comment: *Pasteurella multocida*, the causative agent of fowl cholera, remains a major problem of poultry worldwide.[4] Disease manifestation can range from a mild localized infection to peracute systemic disease with high mortality.[2] The peracute forms are characterized by septicemic lesions, with petechial and ecchymotic hemorrhages in the fat and mucus membranes and necrosis of the liver and spleen.[2] The chronic form often involves the respiratory system as fibrinonecrotic pneumonia, but arthritis, peritionitis, and salpingitis also occurs.[2] Additionally, fibrinonecrotic dermatitis is observed in turkeys and broiler chickens (see 2011 WSC Conference 21, Case 1).

While all types of poultry are considered vulnerable to infection with *P. multocida*, there are species and age differences in susceptibility. Turkeys and waterfowl are considered the most

susceptible species while chickens are more resistant. All birds under 16 weeks of age also appear fairly resistant, though this effect is less pronounced in turkeys.[2]

Necrotizing myocarditis is not a typical finding with fowl cholera, allowing conference participants to review differentials for such a lesion in poultry. Specifically to ducks, *Riemerella anatipestifer* is a frequent cause of polyserositis including pericarditis in young ducklings of intensive production systems. *Salmonella pullorum* causes peritonitis and death in hatchling chicks or peritonitis, arthritis and pericarditis in adults. Coliform infections may lead to myocarditis, but usually with more abundant heterophilic inflammation and fibrin than present in this case. West Nile virus may perhaps be the best differential for necrotizing myocarditis of many avian species, with young chickens and geese being most likely to develop clinical disease and mortality.[1]

Contributing Institution: www.alpc.ar.gov

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CASE II: D13-042840 (JPC 4048790).

Signalment: Adult female bald eagle, *Haliaeetus leukocephalus.*

History: This animal was admitted to The Raptor Center of the University of Minnesota on September 19, 2013. The animal was underweight and unable to fly. It had neurologic signs including nystagmus and muscle tremors. Blood lead levels were low. The animal was euthanized one day after admission due to a grave prognosis for survival and rehabilitation.

Gross Pathology: The animal was moderately underweight. There was marked bilateral symmetrical pan-necrosis of the caudal third of the cerebral hemispheres with collapse of the parenchyma and increased quantity of cerebrospinal fluid ("hydrocephalus ex vacuo") when compared to a control brain of a bald eagle.

Laboratory Result: Cerebrospinal fluid and brain samples were positive for West Nile virus (WNV) and negative for Saint Louis encephalitis virus by PCR (performed at the Animal Health Diagnostic Center of Cornell University). West Nile virus antigen was detected in the cerebrum and retina by immunohistochemistry using a monoclonal antibody specific for the E protein of WNV (clone 7H2, Bioreliance).

Histopathologic Description: Both slides (C and D) are cross sections of the caudal aspects of cerebrum at around the level of the optic chiasm (with the more rostral aspect of the thalamus) and had similar histologic features. The lateral ventricles were dilated.

There was bilateral symmetric pan-necrosis of the gray matter of the dorsal aspect of the cerebral hemispheres ("pallium") along the lateral ventricles. The neuroparenchyma was collapsed and cavitated around what appeared to be a remaining scaffold of vasculature. The neuroparenchyma was largely infiltrated and replaced by numerous macrophages with gitter cell morphology in the pallium. In addition, there was a widespread massive lymphoplasmacytic perivascular infiltration. The endothelial cells were hypertrophied. Numerous cells contained basophilic granular material (interpreted to be calcified mitochondria) and occasional neurons were entirely calcified.

The gray matter adjacent and subjacent to the necrotic parenchyma was hypercellular. The hypercellularity was due to infiltration with lymphocytes and macrophages and due to infiltration by reactive astrocytes. These astrocytes were plump, had an increased amount of a faint eosinophilic cytoplasm and one and occasionally two enlarged vacuolar

2-1. Cerebrum, bald eagle: Brain of a female adult bald eagle (Haliaeetus leukocephalus; dorsal aspect), with control brain on left: There was marked bilateral symmetrical pan-necrosis of the caudal third of the cerebral hemispheres with collapse of the parenchyma. There was an increased quantity of cerebrospinal fluid ("hydrocephalus ex vacuo") that partly was collected for further testing and partly drained as the brain was removed from the brain cranial vault. (Photo courtesy of: Veterinary Population Medicine Department, 244 Veterinary Diagnostic Laboratory, 1333 Gortner Ave, St Paul, MN 55108, www.vdl@umn.edu)
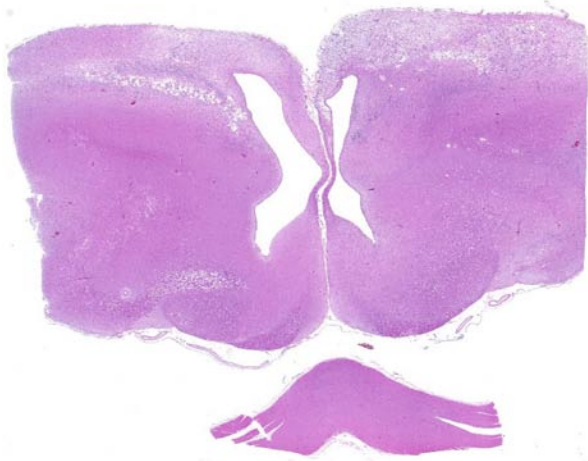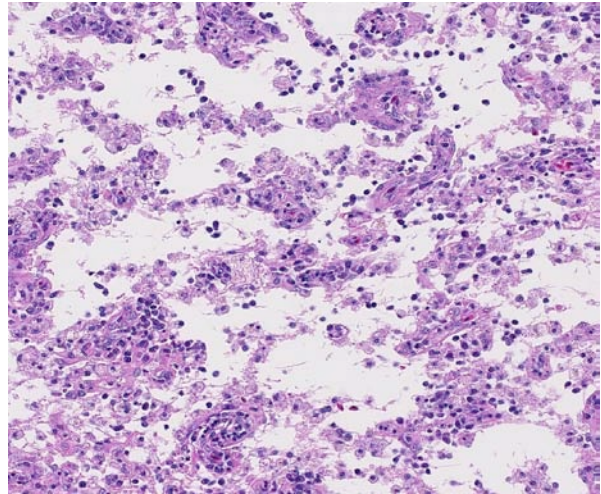
2-2. Cerebrum, bald eagle: There is bilateral asymmetric necrosis and cavitation of the subpial grey matter in the dorsal aspect of the telencephalon, with bilateral distention of the third lateral ventricles. (HE 50X)

2-3. Cerebrum, bald eagle: There are large asymmetrical areas of cavitary necrosis with remnant gliofibrillary strands separated by numerous Gitter cells. (HE 164X)

("euchromatic") nuclei. Occasionally distinctly eosinophilic globules were present in the gray matter (interpreted to be spheroids).

White matter tracts such as the occipitomesencephalic tracts and optic tracts had a bilateral symmetric spongiform change characterized by the presence of numerous optically empty spaces ("interpreted as myelin sheath edema"). In addition, mild to moderate infiltrates of lymphocytes and plasma cells were present around capillaries of the white matter.

Contributor's Morphologic Diagnosis: Brain (cerebrum and thalamus), polioencephalitis, lymphoplasmacytic and histiocytic, chronic, marked with cerebral pan-necrosis and dilation of lateral ventricles ("hydrocephalus ex vacuo").

Contributor's Comment: The lesions were highly suggestive of an ischemic injury or massive viral encephalitis. A protozoal encephalitis (e.g. *Sarcocystis falcatula*) seemed to be unlikely based on the absence of protozoal organisms in the HE-stained sections although protozoal encephalitis cannot be ruled out entirely.[7] West Nile virus (WNV) is a member of the Japanese encephalitis and Saint Louis encephalitis antigenic complex (family: *Flaviviridae*). The virus is primarily transmitted by mosquitoes, but direct contact with infected animals and via oral uptake of virus infected tissues have also been reported. Raptors including bald eagles are frequently infected by WNV and succumb to West Nile disease.[1,4]

Gross lesions of WN disease in bald eagles may include macroscopically appreciable cerebral pan-necrosis as in the presented case in approximately half the cases and in individual cases may include myocarditis and endophthalmitis.[10] The presence of a triad of histopathological changes including encephalitis, endophthalmitis, and myocarditis are a hallmark of WN disease in bald eagles and other Accipitridae including Cooper's hawks (*Accipiter cooperi*), red tailed hawks (*Buteo jamaicensis*), and goshawks (*Accipiter gentilis*).[5,8-10] The pathogenesis of the cerebral pan-necrosis may include a vasogenic component due to damage of endothelial cells by the virus during an early phase of the infection or due to damage of the capillary integrity in the wake of the inflammatory response by extravasating inflammatory cells. Overt WNV-associated arterial necrosis has been described in kestrels and other falcons but does not appear to be a prominent feature of WN disease in hawks and eagles.[4,12] Alternatively or concurrently, the pathogenesis of the pan-necrosis may include direct cytolysis by the virus targeting neurons and possibly glial cells and/or cytolysis of neurons and glial cells as a result of bystander injury in the context of the antiviral immune response. High WNV antigen concentrations are present in the cerebrum (and cerebellum) of bald eagles with fairly acute WNV-associated encephalitis.[10] The cerebral necrosis was similar to a lesion described in one pigeon that was experimentally infected with highly pathogenic avian influenza virus.[2]
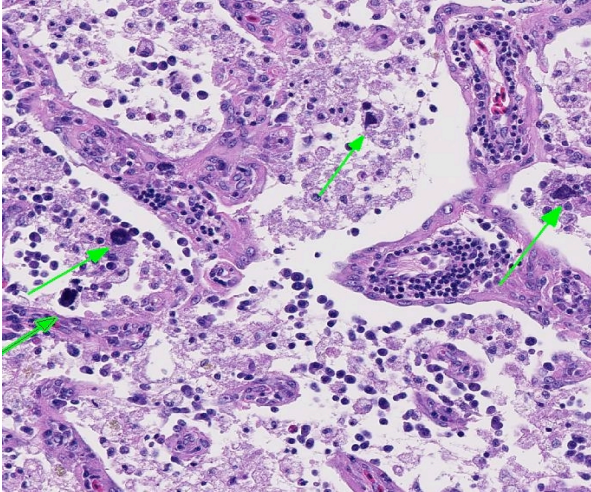
2-4. Cerebrum, bald eagle: Multifocally throughout necrotic and inflamed neuropil, neurons and glial cells are replaced by crystalline mineral (arrows). (HE 164X)
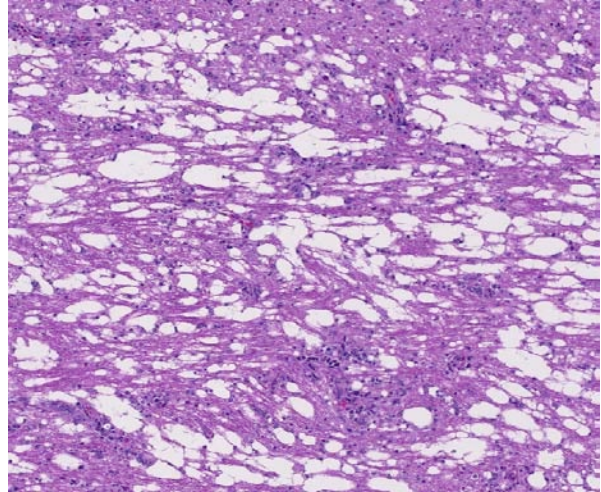
2-5. Cerebrum, bald eagle: There is extensive spongiosis of white matter tracts. (HE 50X)

Based on immunohistochemical analysis, brain (cerebrum and cerebellum), eyes (retina) and to a lesser extent heart and kidney harbor viral antigen similar to findings in other *Accipitridae*. PCR of brain tissue commonly yields a positive result in bald eagles with West Nile disease except for cases that had a significantly prolonged disease, e.g. because they were kept and cared for at a rehabilitation facility for months. In these animals, detection of WNV-specific antibodies in the CSF may be helpful to confirm WN encephalitis.[10]

JPC Diagnosis: Brain: Encephalitis, necrotizing, bilateral, severe, with lymphoplasmacytic perivascular cuffing, white matter spongiosis, mineralization and hydrocephalus *ex vacuo*.

Conference Comment: This is an exceptional example of West Nile virus (WNV), the arthropod-borne *Flavivirus* which utilizes many avian species as a natural reservoir. WNV is found throughout the world and is spread among the migratory bird population. Passeriformes are considered most susceptible to disease, to include the American crow, the blue jay, and the American robin. WNV is maintained in a silent mosquito-bird cycle in natural habitats until introduced into humanized areas where it cycles through humans and horses. This cycle accompanies a seasonal cycle, as the earliest infections arise in late spring and taper off in the fall. Human and horse cases are usually preceded by a few weeks of avian mortalities.[1]

WNV has a wide range of tissue tropism, thus there are no pathognomonic macroscopic lesions. Multiorgan hemorrhages are most characteristically found, and specifically to raptors, cerebral atrophy and malacia is often observed. Microscopically, lymphoplasmacytic and histiocytic inflammation, necrosis, and hemorrhage occur most commonly in the CNS, heart, kidney, spleen and liver. Paradoxically, the most susceptible species have the least amount of inflammation, and raptors that contract more chronic disease develop the triad of lesions described by the contributor.[1]

WNV contains two envelope glycoproteins, E1 and E2, which facilitate tropism for specific tissues.[11] Neuroinvasion requires crossing the blood-brain barrier and may be assisted by the release of proinflammatory cytokines.[11] The chemoreceptor CCR5 contributes to neuroinvasive resistance in humans, as those with CCR5 mutations have an increased rate of symptomatic infection, though this link has not been identified in animals.[3]

Contributing Institution: Veterinary Diagnostic Laboratory, University of Minnesota, www.vdl@umn.edu

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CASE III: BB1705/10 (JPC 4002420).

Signalment: 14-year-old neutered male long-haired domestic cat, *Felis catus*.

History: The owner noticed a large, painless mass on the gingiva, which was surgically resected 6 days later at the local veterinary practice. The biopsy was sent to the R(D)SVS Veterinary Pathology Unit for histological examination.

Gross Pathology: Submitted for histological examination was a gingival lesion, lateral and adjacent to the left maxillary, third premolar tooth. This lesion was a 2cm x 1.4cm x 1.1cm, white nodule that was a little gritty and moderately firm. On cut section, it was homogeneous and white with a small number of irregular dark red areas.

Histopathologic Description: Gingival lesion (4 sections, slides A1 and A2): The submucosa is expanded and effaced by a densely cellular, poorly demarcated and locally invasive proliferation of epithelial cells arranged in anastomosing cords, ribbons and islands within a collagenous stroma. In this surrounding stroma there are moderate numbers of loosely spaced spindle cells. The cells at the periphery of the islands tend to palisade and range from cuboidal to low columnar. They have poorly defined cell borders, a small amount of basophilic cytoplasm, and a central, oval to indented nucleus with finely stippled chromatin and one nucleolus. The cells at the centre of the islands are stellate, with fibrillar cytoplasmic projections, indistinct cell borders and similar nuclear features to those described above. There is mild anisocytosis and anisokaryosis and mitotic figures average 2 per 10 high power fields (400X). Within the centre of many of the larger islands there are circular to globular aggregates of brightly eosinophilic, smudged to glassy, acellular and amorphous material which stains orange/red with apple green birefringence using a Congo red stain (amyloid). Some islands contain central squamous epithelial cells with associated refractile, lamellar, eosinophilic material, consistent with keratin. Cystic spaces within several islands are compatible with cystic degeneration and contain small numbers of neutrophils. A small number of small, irregular, deposits of eosinophilic material are superimposed with deeply basophilic material (mineralized bone, presumptive). The overlying mucosa is multifocally lost (ulcerated), with associated intense neutrophilic infiltration. Within the superficial submucosa there are clusters of lymphocytes and plasma cells, with neovascularisation and edema.

Contributor's Morphologic Diagnosis: Amyloid-producing odontogenic tumor with extensive mucosal ulceration - left maxillary gingival.

Contributor's Comment: Amyloid-producing odontogenic tumors fall into the category of tumors of odontogenic epithelial origin which do not produce odontogenic mesenchyme.[2] Pertinent
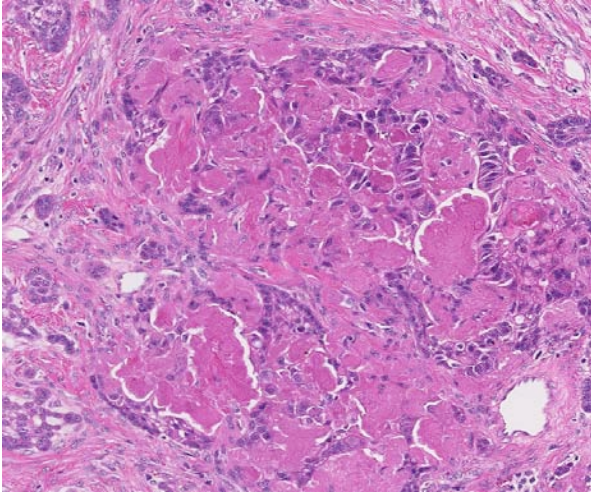

3-1. Gingiva, cat: The gingiva contains a large, well demarcated neoplasm composed of islands and trabeculae of neoplastic cells. (HE 5X)
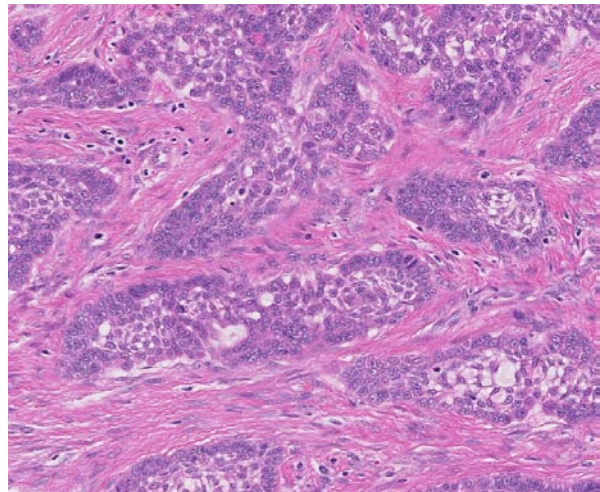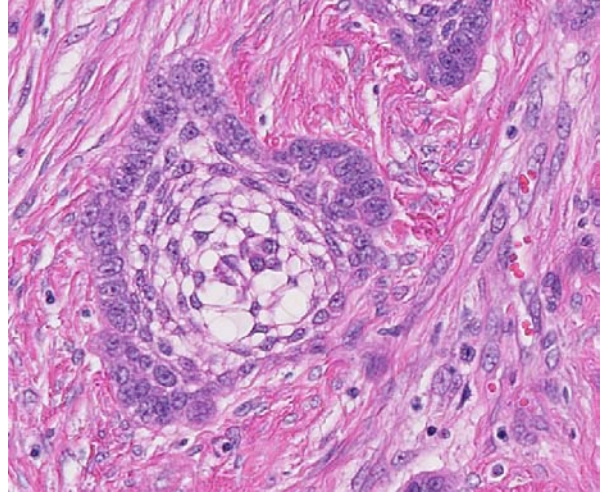

3-2. Gingiva, cat: Islands and trabeculae of neoplastic cells are composed of numerous palisading columnar cells with prominent nuclei. (HE 150X)

3-3. Gingiva, cat: Occasionally, neoplastic cells surround a central focus of loosely arranged small spindle to stellate cells on a pale myxomatous matrix (stellate reticulum). (HE 260X)

3-4. Gingiva, cat: Occasionally, neoplastic cells surround a central focus of loosely arranged small spindle to stellate cells on a pale myxomatous matrix (stellate reticulum). (HE 260X)

histological features include: Anastomosing cords and/or islands of odontogenic epithelium; peripheral palisading of those cells; apical crowding of the nucleus in the palisading cells; and loosely packed internal cells connected by long intercellular bridges, otherwise known as "stellate reticulum"; formation of extracellular deposits of eosinophilic glassy matrix in spherical nodular aggregates.[5]

In this case, the overlying mucosa is ulcerated, with associated neutrophilic infiltration. Additionally, there is accumulation of smudged, pale eosinophilic hyaline material, both within the islands and cords as well as between them. This material is consistent with amyloid, as it stains strongly with Congo red, and is pale green under polarized light.[10]

Amyloid-producing odontogenic tumors (APOT) have been described in dogs, cats and a Bengali tiger.[8-10] They have been reported as focally extensive, infiltrating, firm to friable lesions, frequently involving the entire maxilla.[2,8] These tumors are slowly progressive, locally invasive and can recur locally after excision.[11] There are no reports of metastasis of APOT in the literature.[4]

The histological feature that sets APOTs apart from ameloblastoma and acanthomatous ameloblastoma is the accumulation of amyloid between neoplastic epithelial cells. Other features are shared between these tumors.[5] Recently, the amyloid found in a single case of feline APOT

was typed as odontogenic ameloblast-associated protein (formerly termed APin).[2]

Ultrastructurally in APOTs, cords and islands are delimited by a basement membrane, to which cuboidal to polygonal cells attach by hemidesmosomes. There are also numerous desmosomes between adjacent cells (consistent with epithelial cells). All these cells contain numerous tonofilaments, and pseudoinclusions containing 10nm thick filaments are occasionally noted. The ultrastructural presentation of the amyloid noted on light microscopy consists of intercellular accumulations of haphazardly arranged, non-branching, 10nm diameter filaments, which are frequently in direct contact with the epithelial cells.[3]

With regards to terminology APOTs have been designated calcifying epithelial odontogenic tumors in the past.[4] This designation has fallen out of favor, as this term is used to name an odontogenic tumor in humans that has a different histological presentation. Calcifying epithelial odontogenic tumors in humans frequently contain sheets of polyhedral cells, with extracellular mineralization of amyloid deposits and intracellular mineralization. Although these features are present in APOTs of dogs and cats, they are rare.[5]

JPC Diagnosis: Gingiva, left maxillary: Amyloid-producing odontogenic tumor.
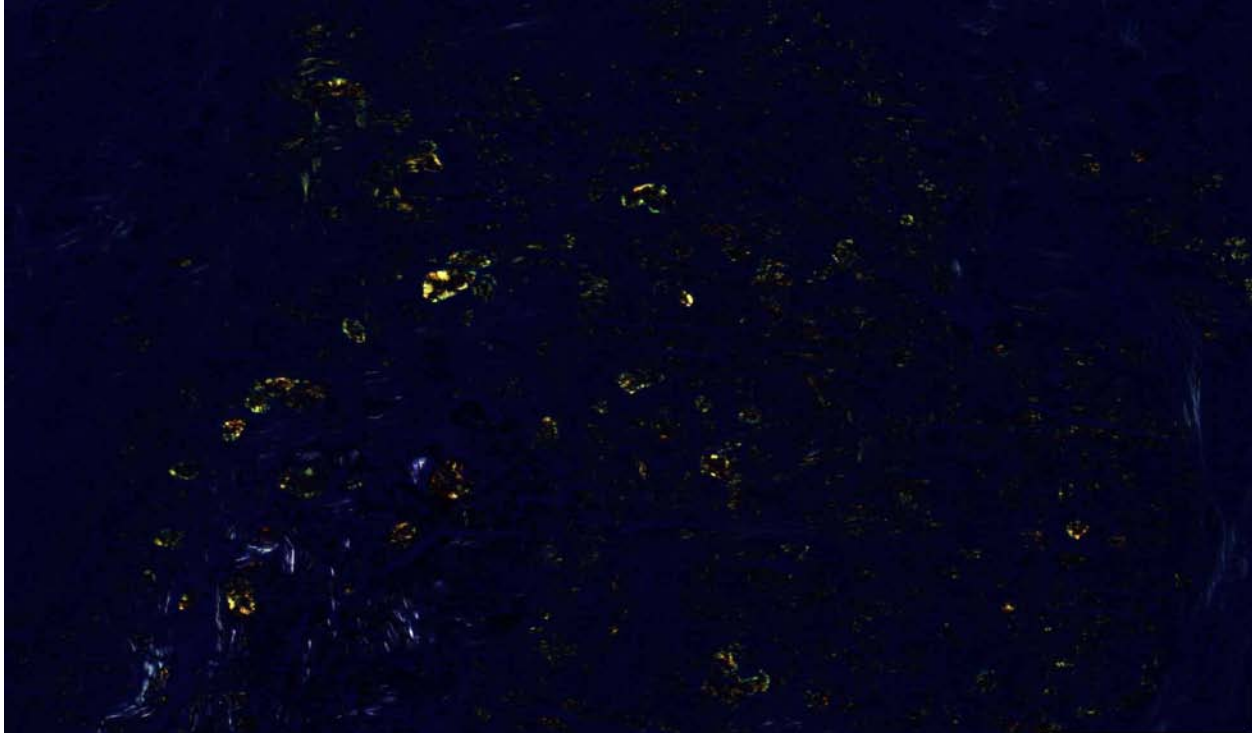
3-5. Gingiva, cat: Congophilic islands of amyloid demonstrate apple-green birefringence under polarized light. (Photo courtesy of: Veterinary Pathology unit, Division of Veterinary Clinical Sciences, Roslin Institute and Royal (Dick) school of Veterinary Studies, The University of Edinburgh, Easter Bush Veterinary Centre, Roslin, Midlothian, EH25 9RG, UK http://www.ed.ac.uk/schools-departments/vet/services/pathology). (Congo Red, 200X)

Conference Comment: Odontogenic tumors of dogs and cats are considered a diverse group of entities often with overlapping and controversial nomenclature. Amyloid-producing odontogenic tumors (APOT), calcifying epithelial odontogenic tumors (CEOT), and keratinizing ameloblastoma share all of the following features: benignity, odontogenic epithelium, and potential for both keratinization and amyloid deposition.[1] The amyloid in APOT has been demonstrated to be derived from ameloblasts, lending credence to its reclassification as amyloid-producing ameloblastoma.[7] The subjective distinguishing criteria and overlapping microscopic features indicate the possibility that all three of these oral tumors may be variants of a single entity.[1]

The majority of, if not all, odontogenic tumors can fit into one of three categories: epithelial, mixed or inductive, and mesenchymal. All of the various manifestations of ameloblastoma, including canine acanthomatous ameloblastoma, solid/multicystic ameloblastoma and the tumors previously discussed are epithelial derived. Mixed or inductive tumors consist of ameloblastic fibroma/fibro-odontoma and feline inductive odontogenic tumors. These are composed of proliferative odontogenic epithelium and odontogenic ectomesenchyme, often with inductive change, and may all occur along a single continuum. Finally, mesenchymal proliferations are perhaps most common, and consist of peripheral odontogenic fibroma (POF) and focal fibrous hyperplasia. The term POF has replaced the use of fibromatous epulis of periodontal ligament origin (FEPLO) among many veterinary surgical pathologists because epulis is a nonspecific term, and the lesion is derived from periosteal stroma rather than periodontal ligament. Both POF and FFH are recognized as separate entities, but also share overlapping clinical and pathologic features.[1]

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http://www.ed.ac.uk/schools-departments/vet/services/pathology

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CASE IV: 10728252 (JPC 3166465).

Signalment: 7-year-old castrated male Chinese Crested canine, *Canis familiaris*.

History: The dog originally presented in March 2009 with an oral gingival mass, mesial to the left mandibular canine tooth and first premolar. The mass was excised and recurred five months later. A partial rostral mandibulectomy was performed in February 2010.

Gross Pathologic Findings: The gingival mass was fluctuant to moderately firm and purple to red.

Histopathologic Description: Oral mucosa, mandible, left lower canine: The submucosa contains an unencapsulated, moderately demarcated, mildly infiltrative multinodular mass with a focal pedunculated region, composed of giant cells on a moderately vascular dense background of spindled stromal cells, interspersed by eosinophilic vascular connective tissue. Giant cells are polygonal to irregular with distinct cell borders, abundant pale basophilic granular to lightly vacuolated cytoplasm and up to 15-20 nuclei. Nuclei are round to oval to irregular with vesicular or finely stippled chromatin and generally one prominent nucleolus. Anisocytosis and anisokaryosis are 2-3 fold and mitoses are 11 in ten 400x high power fields. Scattered through the mass are moderate numbers of macrophages with intracytoplasmic dark tan to light brown granular material (hemosiderin) admixed with moderate multifocal hemorrhage. The overlying epithelium is moderately and diffusely hyperplastic and there is a focally extensive region of full thickness ulceration with replacement by moderate numbers of underlying viable and degenerate neutrophils and a small amount of necrotic cell debris. The superficial submucosa is multifocally edematous, characterized by pale staining and increased space between collagen fibers, and contains frequent thin walled vascular profiles admixed with plump fibroblasts (fibroplasia). Small populations of lymphocytes and plasma cells are noted within the submucosa at the periphery of the mass. The mass does not extend into the underlying bone or adjacent tooth and is completely excised with clean margins.

Contributor's Morphologic Diagnosis: Oral mucosa, mandible, left lower canine: Giant cell epulis with atypia.

Contributor's Comment: The oral mass in this dog was consistent with a giant cell epulis (GCE); however, the stromal spindle cells exhibited inconsistencies with the reported histologic features of this entity. In the stromal spindle cell population, mitoses were observed more frequently than expected for GCE, and anisokaryosis and anisocytosis were observed. Additional differential diagnoses include giant cell tumor of bone and soft parts, osteosarcoma (giant cell variant), or low grade spindle cell sarcoma with giant cells. This mass does not involve or infiltrate bone, contain osteoid, display severe cellular atypia or necrosis and is only present within the oral gingiva, making the first three possibilities less likely. In this case, the atypia observed may represent early neoplastic transformation of the spindle cell population, making differentiation between an atypical variant of GCE and low grade spindle cell sarcoma difficult. Recurrence of this mass may be explained by the incomplete excision of the previous (first) sample, or the presence of the atypical cell populations.

"Epulis" is a non-specific term referring to a benign local exophytic growth of the oral mucosa.[2] Epulides are common in the dog (up to 59% of benign canine oral neoplasms), and canine epulides can be divided into reactive lesions (giant cell epulis, fibrous epulis, pyogenic granuloma and reactive exocytosis) and peripheral odontogenic tumors (fibromatous epulis of the periodontal ligament, acanthomatous epulis (acanthomatous ameloblastoma) and calcifying epithelial odontogenic tumor (amyloid producing odontogenic tumor)).[5,11]

Giant cell epulis (GCE) was reported in a dog as early as 1917 but is a rare lesion, with little information available in the veterinary literature.[4-6,11,12] Classified under "Tumor-like Lesions" in the WHO Histologic Classification of Tumors of the Alimentary System of Domestic Animals, GCE is thought to represent a benign hyperplastic lesion rather than a true neoplastic process.[6,11,12] Despite the low number of documented cases, a variety of canine ages and breeds have been reported, with ages ranging from 1 to 11 years.[5,7,12] These masses arise from gingiva, most often adjacent to

the maxillary and mandibular premolars and are typically red to purple and lobulated.[11,12]

Histologic features of canine and feline GCE are consistent with those reported for human patients.[4] GCE typically presents as a nonencapsulated, poorly demarcated vascular submucosal nodule covered by hyperplastic gingival epithelium that may be ulcerated.[1,2,5,11] Nodules consist of large numbers of randomly distributed multinucleated giant cells in a background of mononuclear stromal cells.[1,7-11] Multinucleated giant cells are irregularly shaped, often containing 10-20 visible nuclei with abundant eosinophilic cytoplasm, and may vary with respect to size (up to and exceeding 100 µm diameter), amount of cytoplasm, nuclear chromatin pattern and prominence of the nucleolus.[1,2,6-8,10,11] Within the giant cell population, cellular and nuclear pleomorphism are not seen and there are few to no mitoses.[2,4,11] The stroma is typically well vascularized and highly cellular, containing numerous round and spindle shaped mononuclear cells that exhibit rare mitoses.[1,2,5-8,10,11] The stroma shows varying degrees of mixed inflammation, as well as frequent hemorrhage, hemosiderosis and occasional osteoid or woven bone deposition.[1,2,5,7,8,10,12]

In the dog, GCE is reported to exhibit slow growth without invasion or metastasis.[4,6,11] Several references have reported no recurrence following removal (post-excision follow-up time ranged from 8-18 months).[5,11,12] In a retrospective study of 52 feline epulides by deBruijin et al (2007), GCE was the second most common type of epulis diagnosed, after fibromatous epulis.[2] In contrast to the behavior of canine GCE, the feline
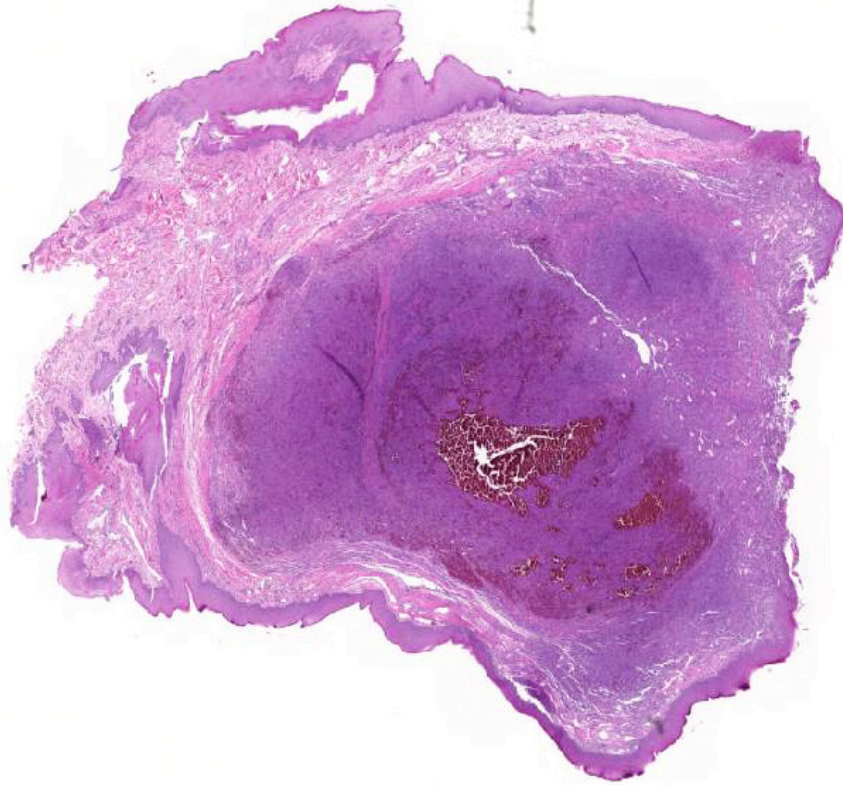
4-1. Gingiva, dog: The gingiva contains an expansile, well-demarcated neoplasm. (HE 4X)

GCE in this study exhibited rapid growth and an aggressive clinical course, with seven out of thirteen recurring within two months of marginal excision.[2] The authors hypothesized that the high recurrence rate and poor prognosis of the GCE in the cat after marginal excision alone may be related to the rapid growth and poor demarcation of the lesion associated with the persistent inflammatory component.[2]

The origin of the multinucleated giant cells in GCE remains unknown. Ultrastructural and immune studies have shown the giant cells to be derived from macrophages, though they are not functional in terms of phagocytosis and bone resorption.[1,11] Due to the close association of GCE with bone, it has been suggested that giant cells are of osteoclast origin, though others have proposed that multinucleated giant cells form by fusion of infiltrating macrophages, as the stroma may contain chronic granulomatous inflammation.[2,4,12] Immunohistochemical studies
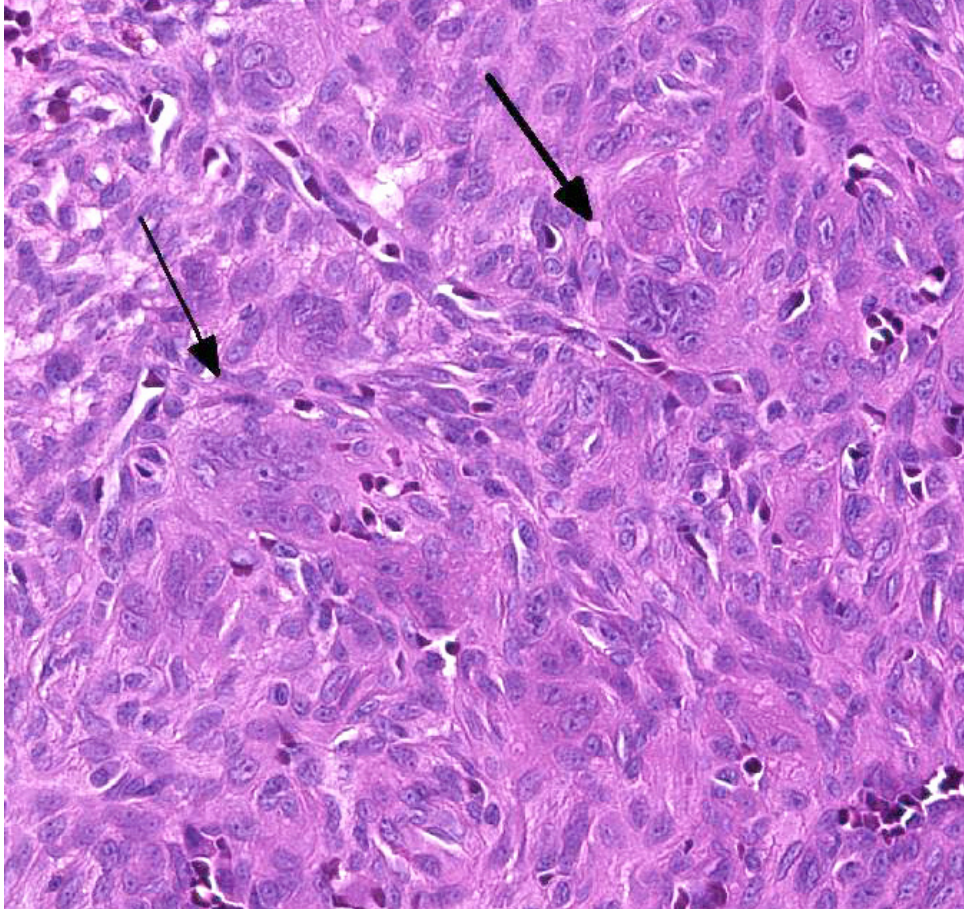
4-2. Gingiva, dog: Neoplastic cells are spindled with prominent nucleoli. There are numerous polygonal multinucleated neoplastic cells scattered thoughout the neoplasm (arrows). (HE 248X)

highest incidence in the fourth to sixth decade of life and the second highest incidence in the first to second decades.[1,8,9,11] It is generally accepted that this mass represents a benign hyperplastic lesion rather than a true neoplastic process, and it is known that chronic trauma or irritation can induce produce granulation tissue with chronic inflammation and fibroblast proliferation and manifest as reactive hyperplasia.[1,9-11] However, the inciting cause of GCE is not known and is controversial, with proposed causes including tooth extraction, poor dental restorations, dental malpositioning, ill fitting dentures, plaque, calculus or food impaction.[1,8-11]

The lesion originates from the connective tissue of the periosteum (mucoperiosteum or periodontal ligament) or from the periodontal membrane and is localized in the interdental papilla, edentulous alveolar margin or at the marginal gingival level.[1,8,10] The mass may involve the mandible or maxilla, though mandibular involvement is approximately 2.5 times more frequent than maxillary, and the premolar and anterior molar regions are most often affected.[1,8-11] Masses vary in size (though rarely exceed 2cm in diameter), are dark red to purple to blue, and can be polypoid, nodular or sessile.[1,8,10] The consistency of the mass depends on age of lesion because as time passes, an increased collagen component leads to increased firmness, and ulceration and bleeding can occur secondary to trauma.[1,8,10]

performed by deBruijn ND et al (2007) indicated that giant cells were strongly positive for vimentin and an osteoclast marker (tartrate-resistant acid phosphatase, TRAP) and negative for factor VIII.[2] Giant cell cytoplasm was also positive for the polyclonal antibody RANK, a cytokine leading to the differentiation of osteoclast progenitors into mature osteoblasts in the presence of its ligand (RANKL).[2] Therefore, the authors hypothesized that the giant cells are most likely formed from a monocyte/macrophage-like osteoclast precursor that differentiates into osteoclasts under the influence of mononuclear osteoblast-like stromal cells.

In humans, this lesion has been known by a variety of names, including peripheral giant cell tumor, peripheral giant cell granuloma, reparative giant cell granuloma, giant cell hyperplasia of the oral mucosa and osteoclastoma.[1,8,10] It accounts for approximately 1% of all oral pathologic lesions and occurs in all age groups, with the

Behavior is variable, with growth ranging from silent to aggressive, affecting adjacent tissues by direct spread, though underlying bone is rarely affected.[1,9] The mass is not usually painful unless there is mucosal ulceration or erosion of the underlying bone, though swelling and dental mobility is common.[1,9,10] Occasional cases in children have been documented to be larger and more aggressive, with local bone destruction, displacement of the adjacent teeth and multiple recurrences.[1,9] Wide surgical excision with extensive clearing of the base of the lesion is usually curative, though when the periodontal membrane is affected, extraction of adjacent teeth may be necessary for full removal.[1,10,11] If resection is only superficial, recurrence is possible, though infrequent (5-11%).[1,8,10,11]

An interesting differential diagnosis in humans is brown tumor; a rare, non-neoplastic reactive growth associated with primary, secondary and/or tertiary hyperparathyroidism.[1,7-10] These masses are solitary or multiple, most often seen on the maxilla, ribs, clavicles and pelvic bones, and the name "brown tumor" is attributed to the gross brown discoloration of the affected tissue due to excessive hemorrhage and hemosiderosis.[6] The growth appears centrally in bone but can perforate the cortical layer, spreading towards the soft tissues, and cannot be distinguished from giant cell epulis based on histology.[1,10] However, this condition is often suspected when there are multiple lesions and recurrences despite adequate treatment.[1,9,10] Interestingly, a report by Headley et al (2008) described the occurrence of an oral lesion with features consistent with brown tumor in a 14-month-old English bulldog with renal secondary hyperparathyroidism due to chronic renal insufficiency.[7]

JPC Diagnosis: Oral mucosa, mandible: Peripheral giant cell granuloma.

Conference Comment: The contributor presents an uncommon proliferative non-neoplastic lesion observed in dogs, cats, and people; and then delivers a comprehensive review as currently understood in the literature. Conference participants observed the vascularization within some areas, and suggested the finding correlated with a reparative lesion.

A recent publication followed 26 diagnosed peripheral giant cell granulomas and concluded they are benign and rarely recur with even marginal surgical excision. Additionally, the number of giant cells and mitotic index of the lesions do not correlate with biologic behavior.[3]

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