**Joint Pathology Center**
**Veterinary Pathology Services**

## WEDNESDAY SLIDE CONFERENCE 2019-2020

# C o n f e r e n c e 21

**3 April 2020**

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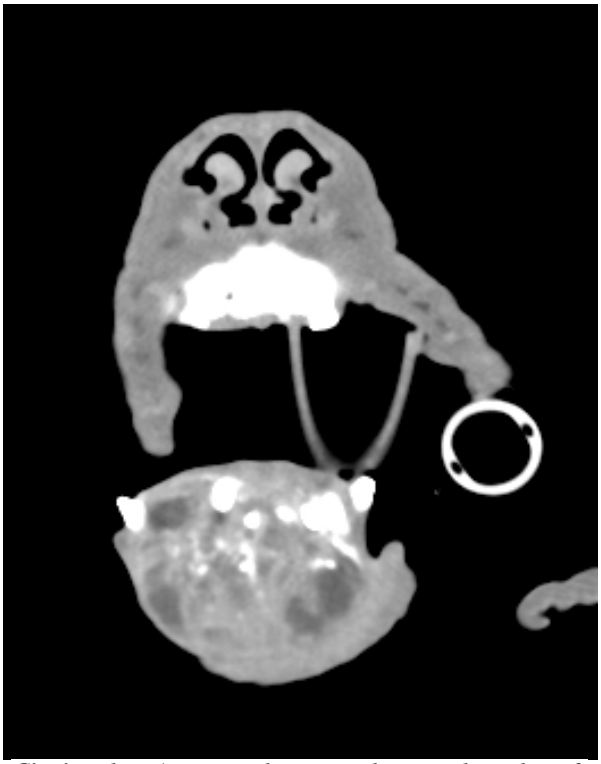
**CASE I:** B-14-0576 (JPC 4066399).

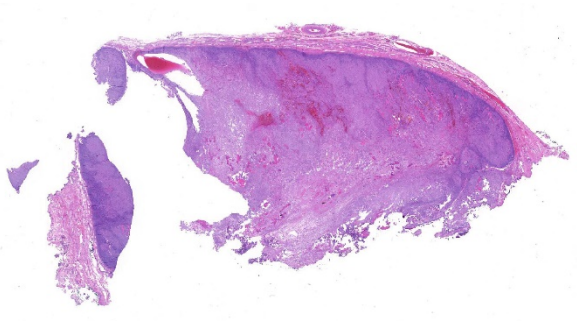
**Signalment:** 9-year-old spayed female Old English sheepdog

**History:** The dog had a one-month history of rostral mandibular swelling displacing mandibular incisors and canine teeth. A previous incisional (Jamshidi) biopsy diagnosis was osteosarcoma. A computed tomography scan showed a soft tissue attenuating mass with pinpoint mineral attenuating foci and heterogeneous contrast enhancement; the mass was markedly displacing teeth and causing marked bony lysis and mild osseous proliferation of the rostral mandible (Fig. 1). The mass and rostral mandible including the tissues rostral to teeth 309 and 409 were removed via mandibulectomy and submitted as a surgical biopsy.



***Gingiva, dog. A computed tomography scan showed a soft tissue attenuating mass with pinpoint mineral attenuating foci and heterogeneous contrast enhancement. (Photo courtesy of: University of Wisconsin-Madison, School of Veterinary Medicine, 2015 Linden Drive, Madison, WI 53706 www.vetmed.wisc.edu)***

**Gross Pathology**: The mandible contained a smooth surfaced mass covered in mucosal epithelium, which extended from just caudal

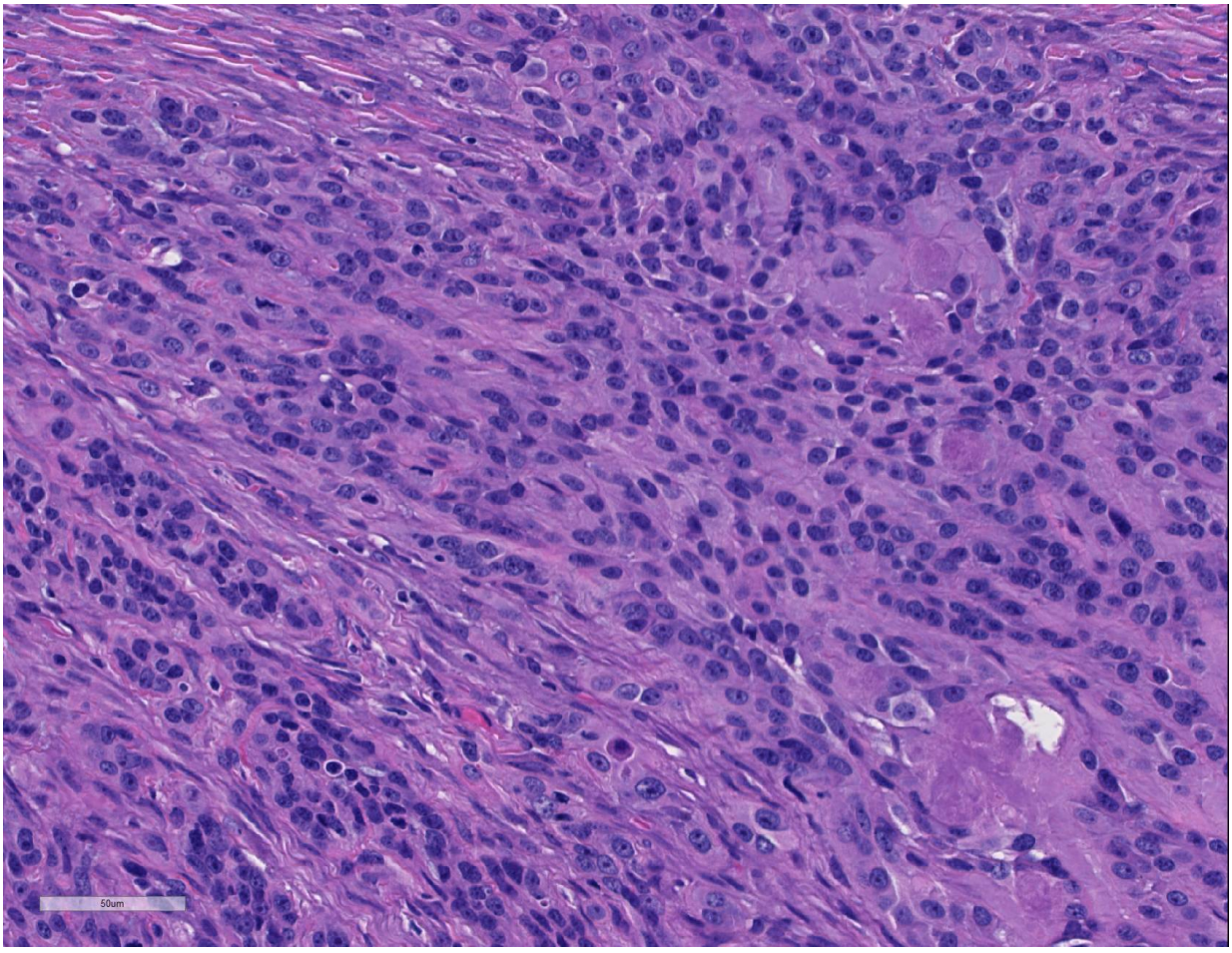


***Gingiva, dog. A well demarcated mass expands the gingiva. (HE, 5X)***

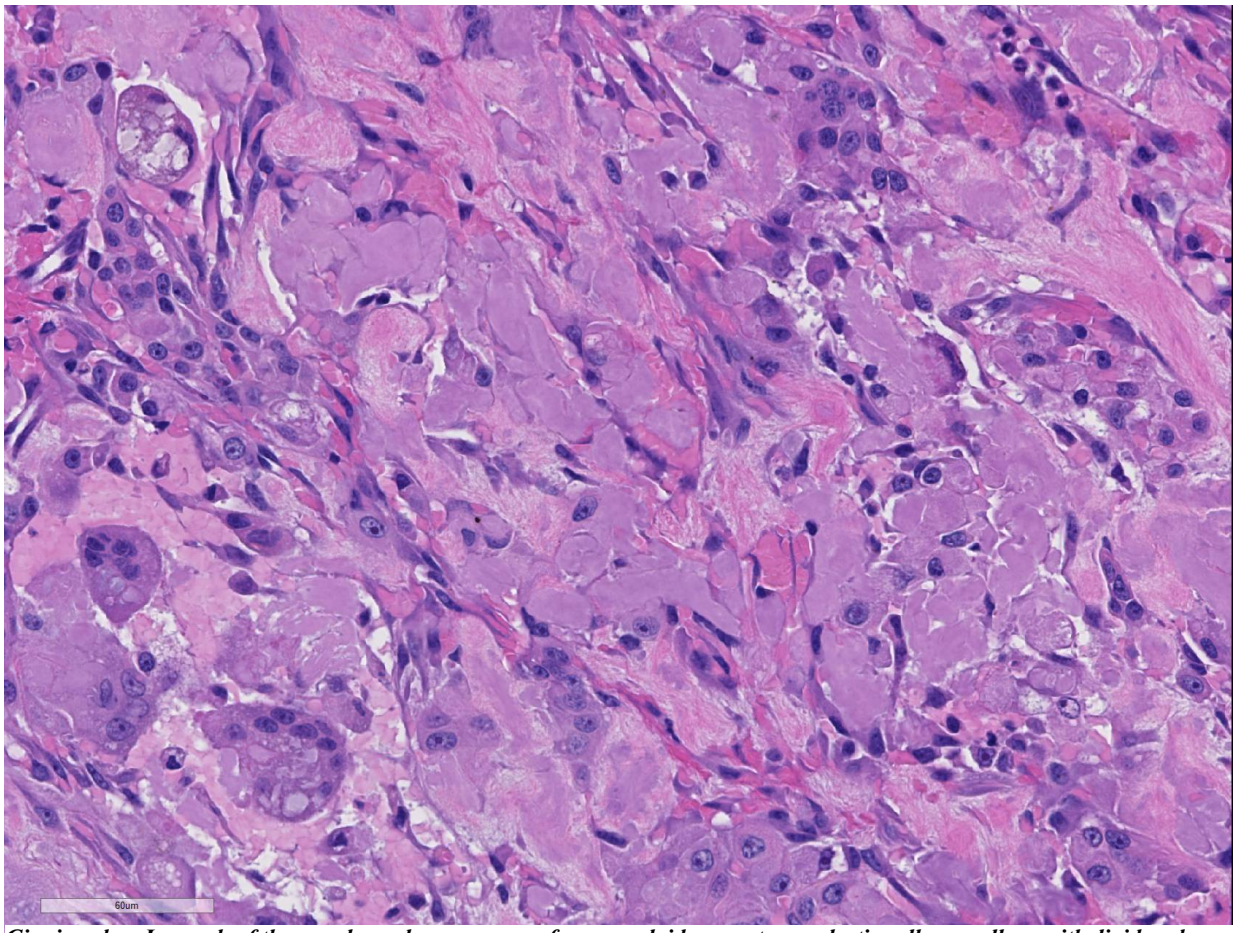
to the canine teeth to rostral to the incisors, expanding tissue between teeth and widely separating the incisors. The mass measured 4.8 x 4.8 x 3.7 cm, and was firm but not hard and lacked bony texture. On midline section the mass was white to red to dark red, with multifocal cavitated areas filled with watery brown fluid. The interior of the mass was soft with no bony texture.

**Laboratory results:** NA.

**Microscopic Description:** The mandible contains and is effaced by an unencapsulated, well-demarcated, multilobulated mass which is composed of polygonal cells arranged in cords,




***Gingiva, dog. Neoplastic cells (which are most dense along the periphery) are cuboidal and form think cords of palisading cells on a moderate fibrous stroma. In this region, small islands of amyloid separate some cords of cells (arrows). (HE, 400X)***




***Gingiva, dog. In much of the neoplasm, large masses of way amyloid separate neoplastic cells as well as epithelioid and multinucleated foreign body type macrophages. (HE, 400jX)***

trabeculae, and few small islands, supported by moderate amounts of fibrovascular stroma and with large amounts of extracellular amyloid. The cells are most dense near the edge of the mass, with increasing amounts of matrix centrally, with some central areas showing fewer neoplastic cells and increased amounts of fibrous connective tissue, or cavities of hemorrhage. The cells have distinct borders with rare prominent intercellular bridges, moderate amounts of eosinophilic cytoplasm, oval nuclei with finely stippled chromatin and 1-2 prominent magenta nucleoli. Anisocytosis and anisokaryosis are moderate. Few binucleate and rare multinucleate cells are noted. Mitotic figures are 2 per ten 400x fields. Many cells contain small to large amounts of amphophilic smudgy amorphous material (intracellular amyloid). In some areas cells are larger with more abundant eosinophilic cytoplasm, which occasionally forms concentric lamellae around the nucleus (keratin).

In many areas, cells are separated by moderate to large amounts of extracellular eosinophilic to amphophilic, smudgy, amorphous material (amyloid). In few areas, the cells are separated by islands and trabeculae of densely fibrillar eosinophilic matrix which has a less basophilic tincture than the amyloid and is often mineralized. There are multifocal areas of hemorrhage or

necrosis, with few large cavities filled with hemorrhage. Centrally there are regions of loose immature fibrous connective tissue containing few islands of neoplastic cells and matrix. Multifocally the mass is surrounded by a band of moderately cellular collagenous connective tissue with evenly spaced stellate cells reminiscent of periodontal ligament; multifocally these regions have many congested blood vessels and few regular trabeculae of woven bone.

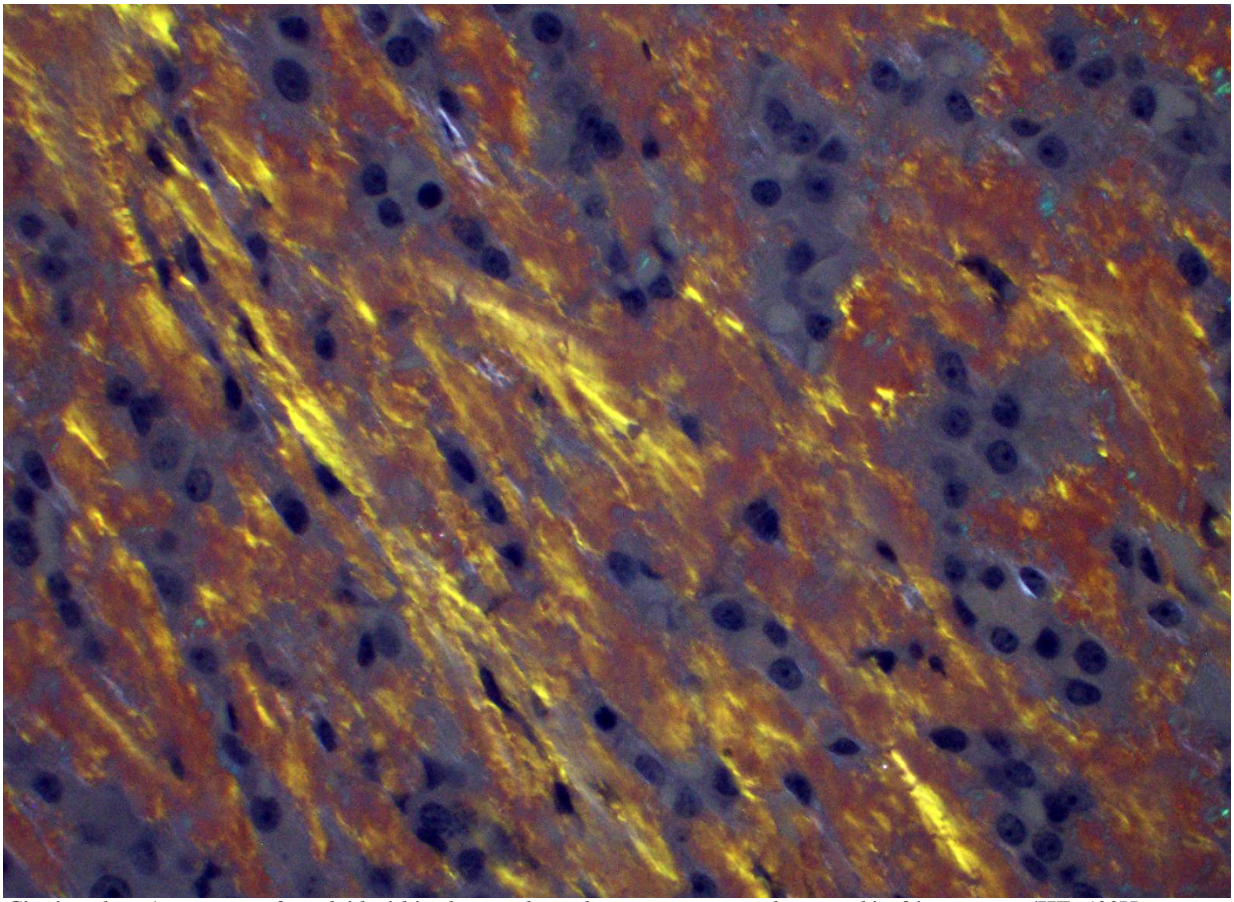
A Congo Red histochemical stain stains the amyloid red, and under polarized light this material has a faint green birefringence.

Pancyokeratin (AE1/AE3) and vimentin immunohistochemistry both show strongly positive cytoplasmic labeling in neoplastic cells. The amyloid is weakly immunopositive for pancytokeratin.

**Contributor's Morphologic Diagnosis:**

Rostral mandible: amyloid-producing odontogenic tumor

**Contributor's Comment:** Amyloid-producing odontogenic tumor (APOT) is a rare neoplasm reported in dogs and cats.[1] Histologically they are characterized by odontogenic epithelium with extracellular and intracellular congophilic amyloid matrix. Features of odontogenic epithelium include thin trabeculae and islands of cells with centrally located cells having long intercellular bridges, and peripheral



***Gingiva, dog. Aggregates of amyloid within the neoplasm demonstrate an apple-green birefringence. (HE, 400X)***

palisading cells with apical nuclei and basilar cytoplasmic clearing. These classical features may be difficult to demonstrate in some tumors, as in this case. Odontogenic epithelium may co-express both cytokeratin and vimentin,[3] as demonstrated in the immunohistochemistry results. Biologic behavior is slowly progressive but metastatic APOT has not been reported. Complete surgical removal is the treatment of choice. The nature of the amyloid protein in this tumor is reported to be a combination of enamel proteins.[2] This tumor has also been referred to as 'calcifying epithelial odontogenic tumor', but the term is borrowed from a human condition with several distinctly different features from APOT, including mineralization of matrix and sheets of polygonal cells.[1,4] APOT is not reported in humans.

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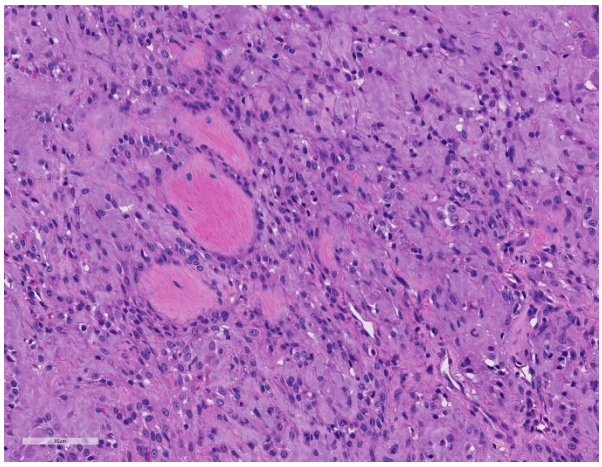
**JPC Diagnosis:** Gingiva: Amyloid-producing ameloblastoma.

**JPC Comment**: Amyloid-producing odontogenic tumors (APOT), are rare tumors of the oral cavity and have been reported in dogs, cats, and in a goat, horse, rabbit, moose, Bengal tiger and a prairie dog.[6,9] These rare tumors have been reported to comprise between 1 and 4% of odontogenic neoplasms in the dog.[8] It has also been recently reported in the facial skin of cats within the supraorbital and labial skin.[4]

This history of this neoplasm has not been without controversy, as evidenced by the many names by which it has been referred to over the years. Originally diagnosed in humans in 1958 by J.J. Pindborg, the neoplasm in many early veterinary texts was referred to as a calcifying epithelial odontogenic tumor (CEOT) or "Pindborg tumor", but a 1994 publication by Gardner et al provided evidence that the human and veterinary versions of the neoplasm were distinct entities and proposed the name amyloid-producing odontogenic tumor.[9] Recent publications have suggested that the CEOT and APOT may be two stages along a spectrum of a tumor which produces a variety of substances such as dental hard substances such as cementum and dentin, amyloid, and keratin[9]. In a recently published textbook on veterinary oral and maxillofacial pathology, the tumor is referred to as an amyloid-producing ameloblastoma.[9]

These neoplasms are unencapsulated neoplasm that may arise either centrally or peripherally within the bone, which while widely considered benign, may aggressively invade bone.[8,9] The tissue or origin is not clear, and current thought of origin include some component of odontogenic epithelium of the dental lamina, stratum intermedium of the enamel organ, or Hertwig's epithelial root sheath.[9] The appearance of the epithelial component may vary widely from traditional columnar to spindled or even round in less differentiated regions of the tumor.[9] Some feline tumors may even have melanin granules within the epithelial component.[9] Pancytokeratin and vimentin may be helpful in differentiating between



***Gingiva, dog. Odontogenic cells occasionally surround islands of dental hard substance within the neoplasm. (HE, 100X)***

epithelial, stromal, and inflammatory components.

The deposition of amyloid is the defining characteristic of this particular neoplasm. Amyloid within APAs has been shown to be different from AA, AL, and senile cardiovascular amyloid.[8] Odontogenic amyloid ameloblast-associated protein (ODAM), a feature of human CEOTs has not been identified within these tumors (supporting their distinction from the human CEOT), a number of other amyloid-related proteins have been found in canine and feline APAs, including amyloid protein of canine APOT, ameloblastin (also present in cat APAs), amelogenin, and sheathlin.[4,8] While the amyloid material in this case demonstrates congophilia and green birefringence on polarized light, the material is not always birefringent.[9] Some authors believe that the amyloid-like material represents dysplastic tooth matrix, as immunohistochemical analysis of the amyloid protein in several studies has indicated that it is of ameloblastic origin.[1, 3]

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**CASE II**: H17-0922-03 (JPC 4122528).

**Signalment:** 4 year-old neutered male rabbit (*Oryctolagus cuni*culus).

**History:** The owner had noticed dysorexia and weight loss. A mandibular mass associated with malocclusion was diagnosed by the attending veterinarian. CT scan showed left mandibular neoplastic infiltration with osteolysis and periosteal reaction but no infiltration of the mandibular lymph nodes.

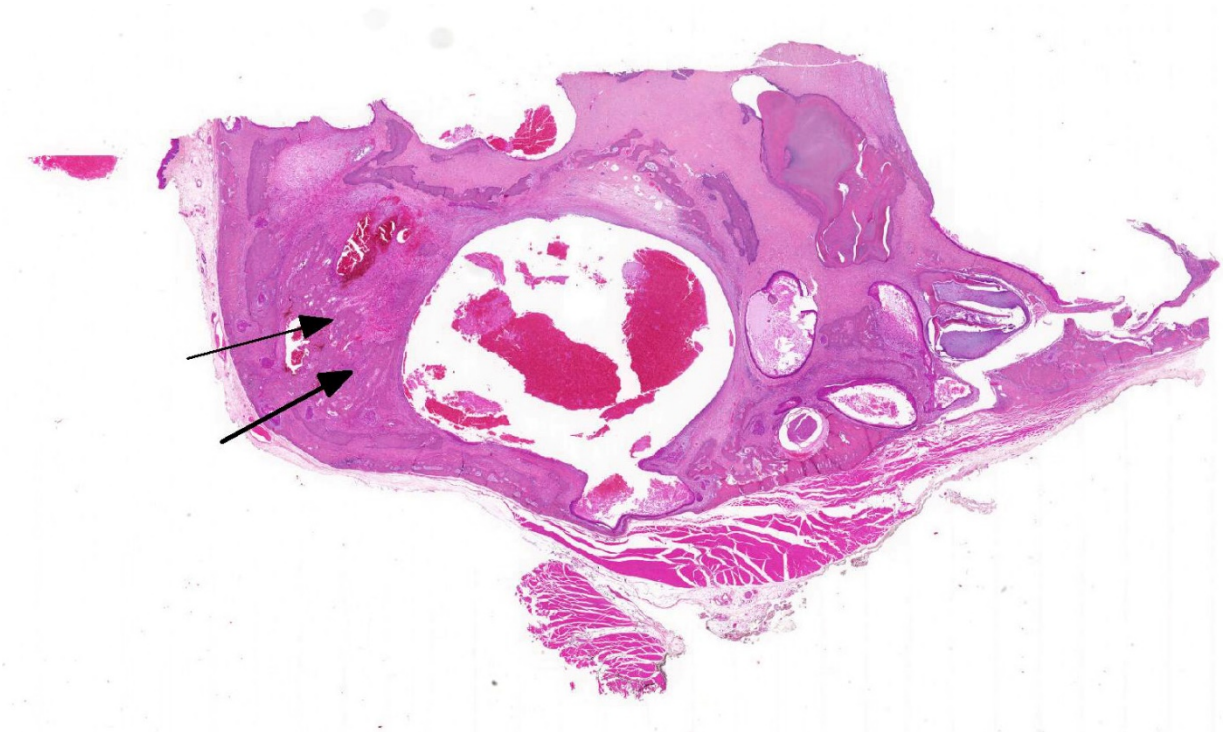
The animal was referred to the Centre Hospitalier Universitaire Vétérinaire d'Alfort (ChuvA) for a surgical exeresis with a left hemimandibulectomy. The animal died of cardiac arrest 30 minutes after the surgery during the recovery phase.

**Gross Pathology**: A non-ulcerated, firm, infiltrating, left mandibular mass measuring 1.5 x 2 cm in diameter with a central depressible zone caused an incisor malocclusion.

**Laboratory results:** NA.

**Microscopic Description:** Gingiva with mandibular bone:

A relatively well-delineated, unencapsulated neoplasm focally infiltrates the mandibular bone. It is admixed with preexisting dental and osseous structures, and is composed of several tissue types. The first is a dense proliferative fibrous mesenchymal tissue composed of fusiform to stellate cells (reminiscent of periodontal ligament) with multifocal osseous metaplasia. The second consists in squamous epithelial nests, sometimes with cystic degeneration (accumulating desquamated cells and red blood cells in the lumen). The third component is an inconstant association of epithelial and mesenchymal structures variably mimicking normal teeth. The best differentiated areas are organized around a loose mesenchyme reminiscent of the dental pulp (ectomesenchyme), covered by a single layer of cubic to columnar cells (odontoblasts) producing an orange tubular matrix (dentin). A hypereosinophilic amorphous material (enamel) lies against the dentin; it is synthetized by a well-differentiated columnar single-layered epithelium with an inverted polarity (apical nuclei and clear basal pole) and forming palisades (ameloblasts). Their apical pole is inconstantly in contact with stellate vacuolated epithelial cells (less differentiated: stellate reticulum). The infiltrated mandibular bone in contact with the tumor is multifocally osteolytic with Howship's lacunae containing osteoclasts and woven bone lined by osteoblasts.



***Alveolar bone, rabbit. The jaw bone (skeletal muscle at bottom) is effaced by a variably cystic neoplasm. Areas of bone lysis and resorption are evident and there is a large area of reactive woven bone formation adjacent to the neoplasm (arrows). (HE, 6X)***

**Contributor's Morphologic Diagnosis:**

Gingiva with mandibular bone: Odontogenic tumor – Complex odontoma

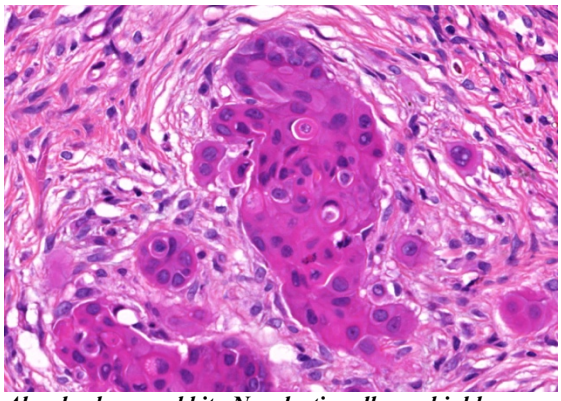
**Contributor's Comment:** Odontogenic tumors are predominantly described in dogs and cats, and are rare in other species.[3,7] Due to their similarities and the complex organization of the teeth, they present a diagnostic challenge. Identification and classification of odontogenic tumors are based on recognizing developing or fully developed teeth tissues or odontogenic epithelium.

Knowledge of odontogenesis and components of teeth is therefore essential.

Teeth develop from two embryonic tissues[8]: oral cavity Malpighian epithelium and embryonic mesenchyme (ectomesenchyme).

At first, a fragment of oral Malpighian epithelium invaginates in embryonic mesenchyme to form the dental lamina. The latter progressively differentiates in enamel organ, an epithelial structure composed by central stellate reticulum, lined by external and internal ameloblastic epithelium (bell stage). The embryonic mesenchyme condenses under the internal ameloblastic epithelium to form the "dermal papilla", the future dental pulp. These epithelial and mesenchymal dental structures have an inductive effect on each other. It is called *reciprocal odontogenic induction*:

1) Internal ameloblastic epithelium promotes the differentiation of the superior part of the dental papilla in an odontoblast layer.



***Alveolar bone, rabbit. Neoplastic cells are highly invasive, forming small nests or islands or simply individual cells surrounded by a schirrous response. Neoplastic cells exhibit occasional keratinization. (HE, 400X)***

2) Odontoblasts secrete dentin which accumulates at the odontoblasts-ameloblasts interface.
3) Presence of dentin is necessary to enamel synthesis by ameloblasts. Enamel accumulates between the dentin layer and ameloblasts.

After odontogenesis, amelobasts degenerate during dental eruption, except in hypsodont species with continuously erupting teeth (such as rodents and rabbits).

The classification and diagnosis of odontogenic tumors is based on the quantity and localization of odontogenic epithelium, production of enamel, and presence or absence of ectomesenchyme (dentin, cementum, mesenchyme resembling the periodontal ligament or the dental pulp). Visualization of dental hard tissue such as enamel, dentin or cementum is helpful in recognizing an odontogenic tumor but is an inconstant finding.[3]

These tumors are separated in three groups:

1) **Tumors with only odontogenic epithelium** (without odontogenic ectomesenchyme):

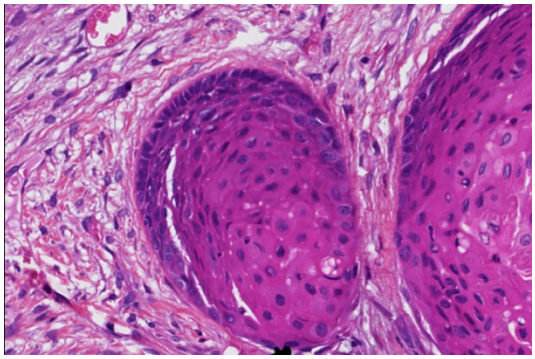
*Ameloblastoma, Canine acanthomatous ameloblastoma, Ameloblastic carcinoma, Amyloid producing odontogenic tumor*

2) **Tumors with mesenchyme and/or odontogenic ectomesenchyme:** *Cementoma/cementoblastoma, Odontogenic myxoma/myxosarcoma, Peripheral odontogenic fibroma (previously called epulis)*

3) **Tumors with odontogenic epithelium and odontogenic ectomesenchyme** (with or without hard tissue):

*Ameloblastic fibroma, Infiltrative inductive ameloblastic fibroma, Ameloblastic fibro-odontoma, ameloblastic Fibro-dentinoma, Ameloblastic fibro-odontosarcoma, Complex odontoma, Compound odontoma.*

In our case, the concurrent identification of dentin, odontoblasts, mesenchyme tissue resembling periodontal or dental pulp (= ectomesenchyme), as well as ameloblasts producing enamel and stellate reticulum (= odontogenic epithelium), confirms this

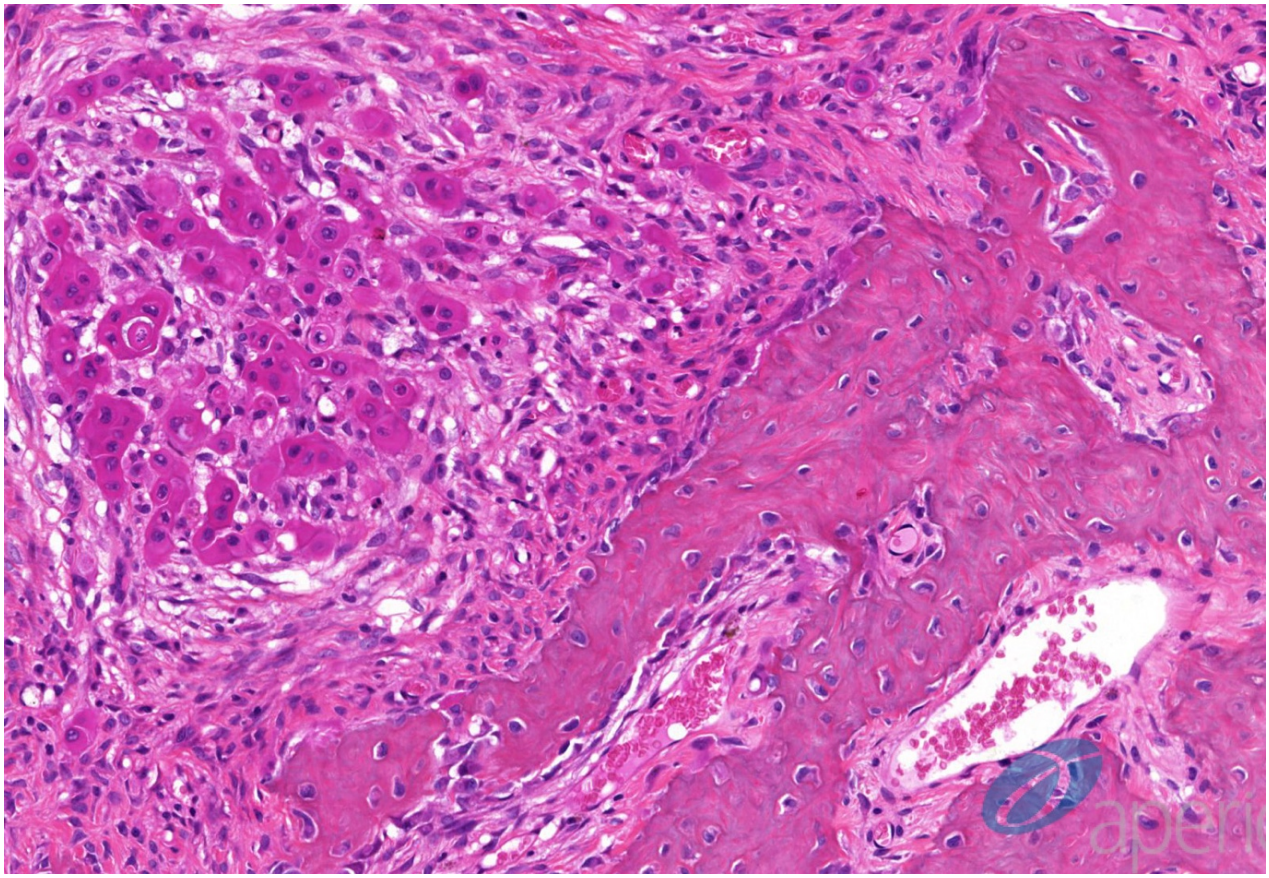


***Alveolar bone, rabbit. Neoplastic cells rarely exhibit odontogenic features, including peripheral palisading and antibasilar nuclei.. (HE, 400XX)***

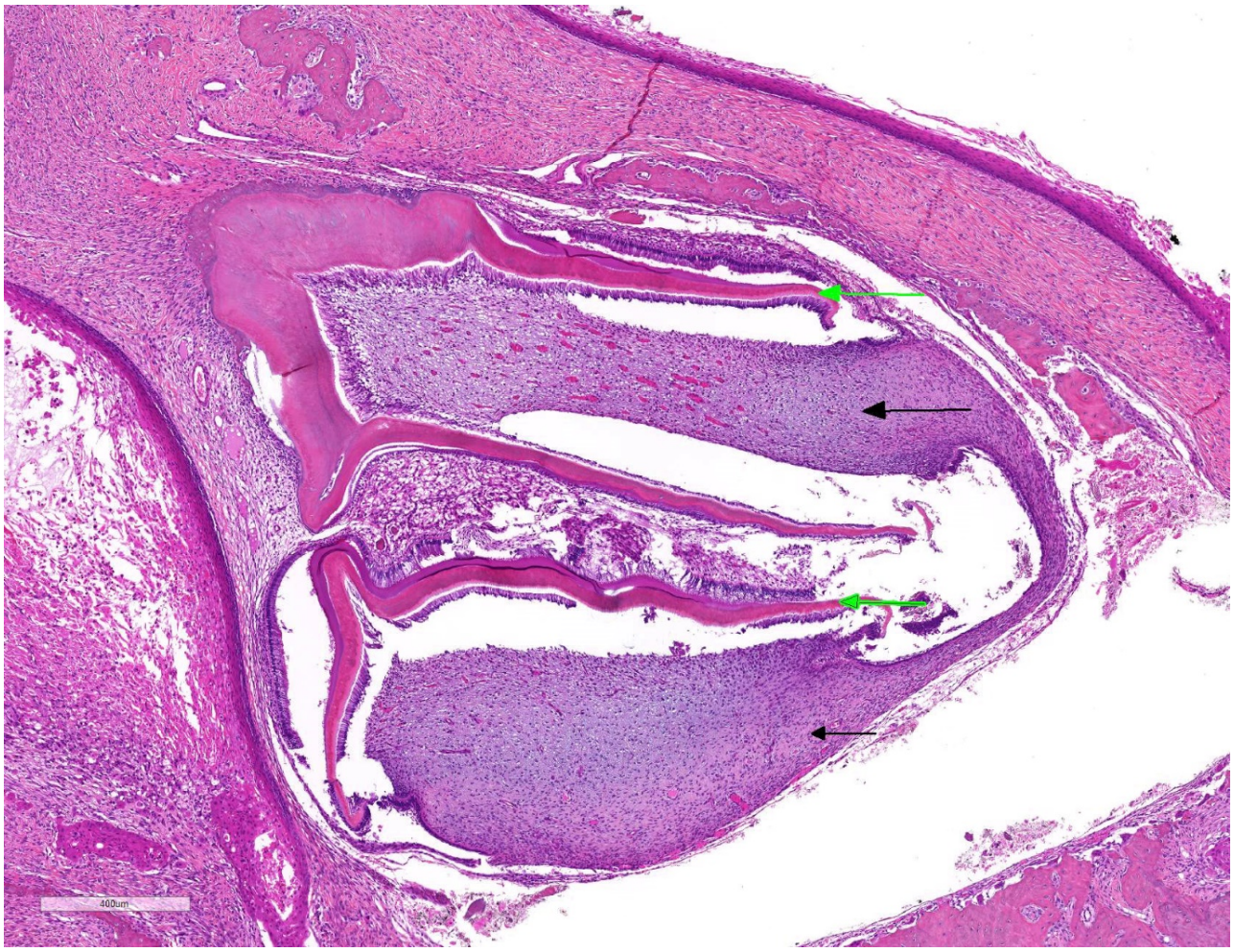
neoplasm as an odontogenic tumor and directs the diagnosis towards a mixed odontogenic tumor. An odontoma is a dental tumor in which cell differentiation has resulted in formation of dentin and enamel. They are two types: *Complex* (poorly differentiated) and *Compound* (well differentiated, with denticle formation) [4] . The apparent disorganization of the odontogenic elements (absence of well-differentiated denticles) leads us to conclude that this particular neoplasm is a complex odontoma.

Complex odontoma are described in horses, dogs, cattle, rats and are located on the mandibular or maxillary arch. The etiology of odontomas is yet not known. Several hypotheses have been formulated: local trauma (and that continuously erupting teeth might be more sensitive to trauma), malocclusion (which may disrupt normal dental eruption), and infection.[1,9]

Furthermore, carcinogens such as methylnitrosourea may induce development of odontomas and other odontogenic tumors in rats.[1,9] In the literature, odontomas are rarely described in rabbits but are well characterized in prairie dogs: this tumor is the third tumor in frequency (9.4%) in that species, after hepatocellular carcinoma (35.8%) and lymphoid tumors (14%); affected animals are between 2 and 6 years



***Alveolar bone, rabbit. Islands of neoplastic cells are surrounded by a schirrous response and abundant proliferative woven bone. (HE, 28X)***




***Alveolar bone, rabbit. The developing tooth is dysplastic with undulant enamel and dentin (green arrows) and widened dental papilla (black arrow), consistent with odontodysplasia. (HE, 51X)***

of age, both maxillary and mandibular arches are affected but animals only display symptoms in maxillary tumors (anatomic proximity with the hard palate, posterior choanae and the posterior nasal meatus).[5]

Distinguishing complex odontoma from ameloblastic fibro-odontoma can be quite challenging. In both cases, diagnosis is based on identifying odontogenic epithelium reminiscent of the enamel organ, a loose odontogenic ectomesenchyme resembling dental pulp, and several types of hard dental tissue (dentin, cementum, enamel). In some case, the diagnostis is not possible by histopathology alone.[3] The age of animal and the type of tooth growth (continuously erupting or not) may be required to refine the diagnosis.

All odontogenic tumors are benign but locally aggressive. Only one case of malignant fibro-odontoma has been described, in a dog.[6] Surgical excision is curative in most cases, but may be quite complex to perform.

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**JPC Diagnosis:** Gingiva and alveolar bone: Carcinoma with odontodysplasia.

**JPC Comment**: In the sections we examined, the primary lesion was composed of a malignant, invasive epithelial neoplasm surrounded by a scirrhous response and woven bone proliferation. These features are consistent with a carcinoma. Potential sources for carcinoma include odontogenic epithelium (i.e. ameloblastic carcinoma; AC) or gingival epithelium (i.e. squamous cell carcinoma; SCC). There is substantial overlap between these diagnoses as both form islands of pleomorphic epithelial cells that can have some keratinization.

Generally, SCC has a greater degree of keratinization, is more inflammatory, and is associated with (potentially ulcerated) gingival mucosa. AC should have some features of odontogenic epithelium and can arise from either the gingival mucosa or deeper in submucosal connective tissue or jaw, without any evident connection to the gingival mucosa.[4] In this case, although both odontogenic epithelial features (there was rare palisading of cells with antibasilar nuclei) and keratinization were present, neither were prominent. Additionally, gingival mucosa was not present in the examined sections and we could not determine if this neoplasm arose from the overlying mucosa. Taken together, we favored a more general diagnosis of "carcinoma with odontodysplasia."

Odontodysplasia (OD) was evident in the developing teeth at the edge of the sections examined. Histologically, OD is a malformation of a tooth (or multiple teeth) or the components of a tooth. It occurs due to trauma to the dental germ during odontogenesis. Dysplastic teeth often fail to erupt.[4] There is substantial histologic overlap between OD and odontoma and distinguishing between these two can be difficult to impossible. The presence of concurrent inflammation/trauma (trauma in this case was from carcinoma with abundant scirrhous response and bony proliferation) should assist the pathologist in diagnosing OD over odontoma.

(A note of thanks to Dr. Brian Murphy of UCDavis for assistance with this very challenging case. His recent volume in oral and maxillofacial pathology was used in the determination of the JPC morphologic diagnosis in all of the cases this week.)

**References:**

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**CASE III**: S2018-0004 (DVD) (JPC 4117676)

**Signalment:** 13 year old, female, Red-tailed boa (*Boa constrictor ortonii*)

**History:** This boa developed a mass along the inner (palatine) left maxillary dental arcade, and despite antimicrobial therapy, it continued to grow. Radiographs demonstrated widening of the bone with lysis. The mass was resected and submitted for histopathological examination.

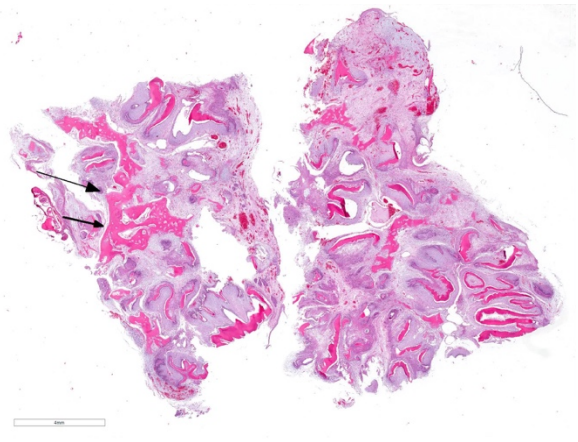
**Gross Pathology**: The sample received was a 3.5 cm x 1.8 cm x 1.4 cm fleshy to firm, oblong, pink to dark red and purple mass with three teeth embedded on one lateral side. On cut section, the mass appeared to extend to the deep margin and was composed of multifocal, tan, soft regions and firm, white, bony regions.

**Laboratory results:** NA.

**Microscopic Description:** Gingiva with mandibular bone:

Oral mass: Expanding the submucosa and raising the overlying mucosal epithelium is a poorly demarcated, unencapsulated, neoplasm composed of epithelial and mesenchymal elements that frequently form haphazardly arranged, variably sized and shaped, tooth-like structures on a moderate fibrovascular stroma. Islands and wavy aggregates of brightly eosinophilic extracellular material with fine tubular

***Head, boa. Pre-operative image of an expansile mass arising from the left maxillary, dental arcade. (Photo courtesy of: Wildlife Conservation Society, 2300 Southern Blvd., Bronx, NY 10460, https://www.wcs.org/)***

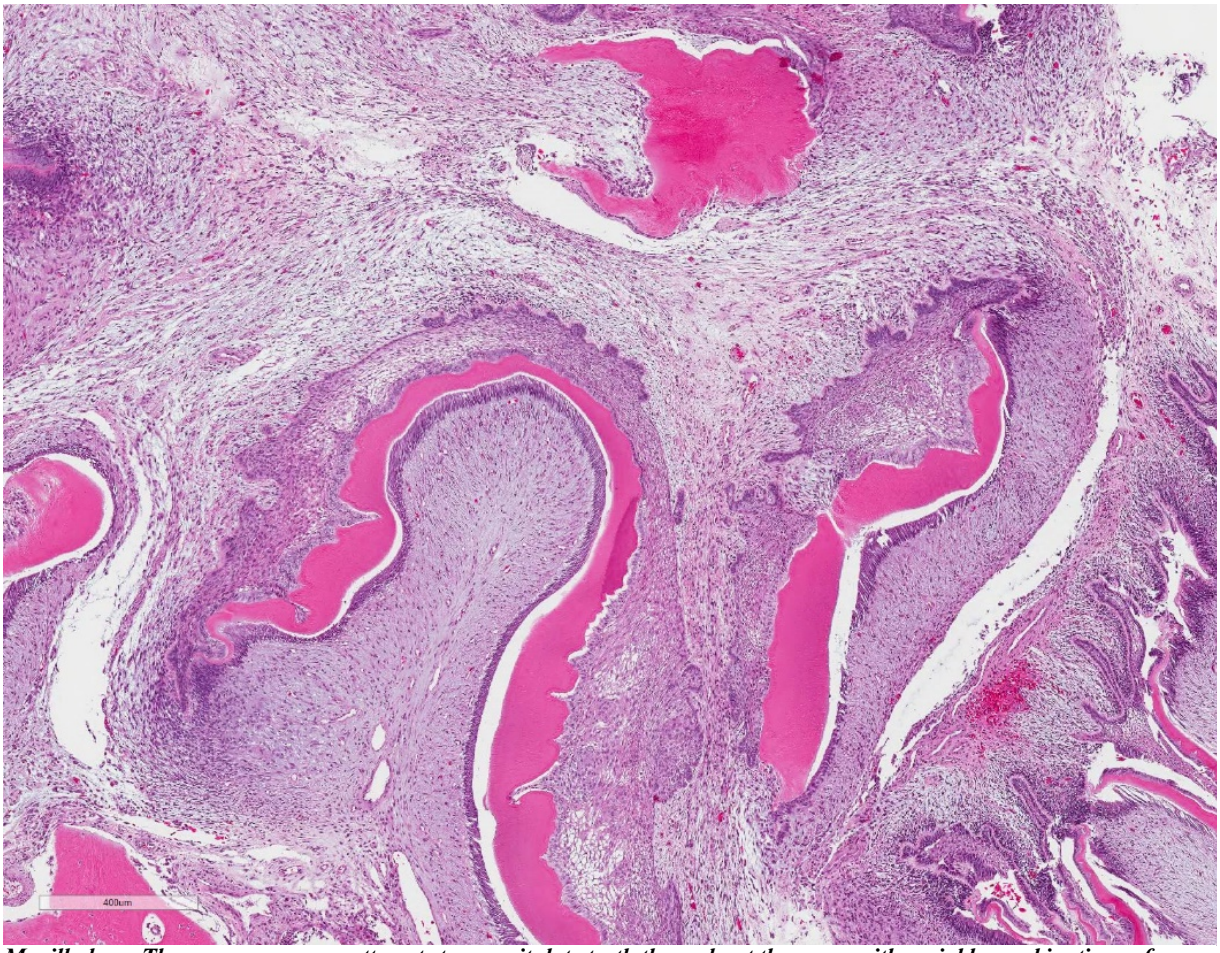


***Maxilla, boa. Two sections of the mass are submitted for examination. Numerous attempts at recapitulating teeth with brightly eosinophilic dentin efface the maxillary bone (arrows). (HE, 7X)***

cavities (dentin) and an occasional adjacent clear gap are surrounded on one aspect by a layer of well-differentiated, palisading odontoblasts and on the other aspect by variably thick rows and sheets of tightly packed columnar to polygonal shaped cells with apically oriented nuclei (ameloblasts). The ameloblasts are often arranged in palisading rows overlying loosely arranged stellate to fusiform cells with prominent intracellular bridging (stellate reticulum). In other regions, odontogenic epithelium is more haphazardly arranged in sheets, small follicles, or branching, anastamosing trabeculae and islands that have a peripheral palisade of cells and infiltrate into the surrounding mesenchyme. Occasionally, islands and trabeculae bud off from rows of ameloblasts bordering dentin material. Within the mass, neoplastic odontogenic epithelium occasionally form cords and nests that are not associated with dentin, with multifocal areas of prominent cellular vacuolation (degeneration) or loss of cells and accumulation of pale, basophilic wispy material admixed with sloughed cells and pyknotic nuclear debris. The neoplastic cells have distinct cell borders with small to moderate amounts of eosinophilic cytoplasm, round to oval nuclei with finely stippled chromatin and one to two, small central nucleoli. There is mild to multifocally moderate anisocytosis and anisokaryosis in this population with 6 mitotic figures in ten 400x figures. Multifocally, neoplastic cells undergo abrupt keratinization. Spindle to stellate mesenchymal cells with an accompanying vascular component (dental pulp) are often present centrally within the tooth-like structures. Infrequently, the eosinophilic dentin material is surrounded by small numbers of multinucleated odontoclasts. Multifocally, there are trabeculae of moderately cellular, woven new bone and small amounts of existing lamellar bone that are occasionally surrounded by small numbers of osteoblasts or small numbers of multinucleated osteoclasts in Howship's lacunae. The overlying mucosa is largely ulcerated and the subjacent submucosa is expanded by increased clear space and pale eosinophilic proteinaceous material (edema). In one section (slide 2), the ulcerated mucosa is covered by a dense band of eosinophilic degenerate material, with small to moderate numbers of granulocytes infiltrating into the subjacent submucosa. Scattered throughout the mass and submucosa are small to moderate numbers of histiocytes, lymphocytes and plasma cells.

**Contributor's Morphologic Diagnosis:**

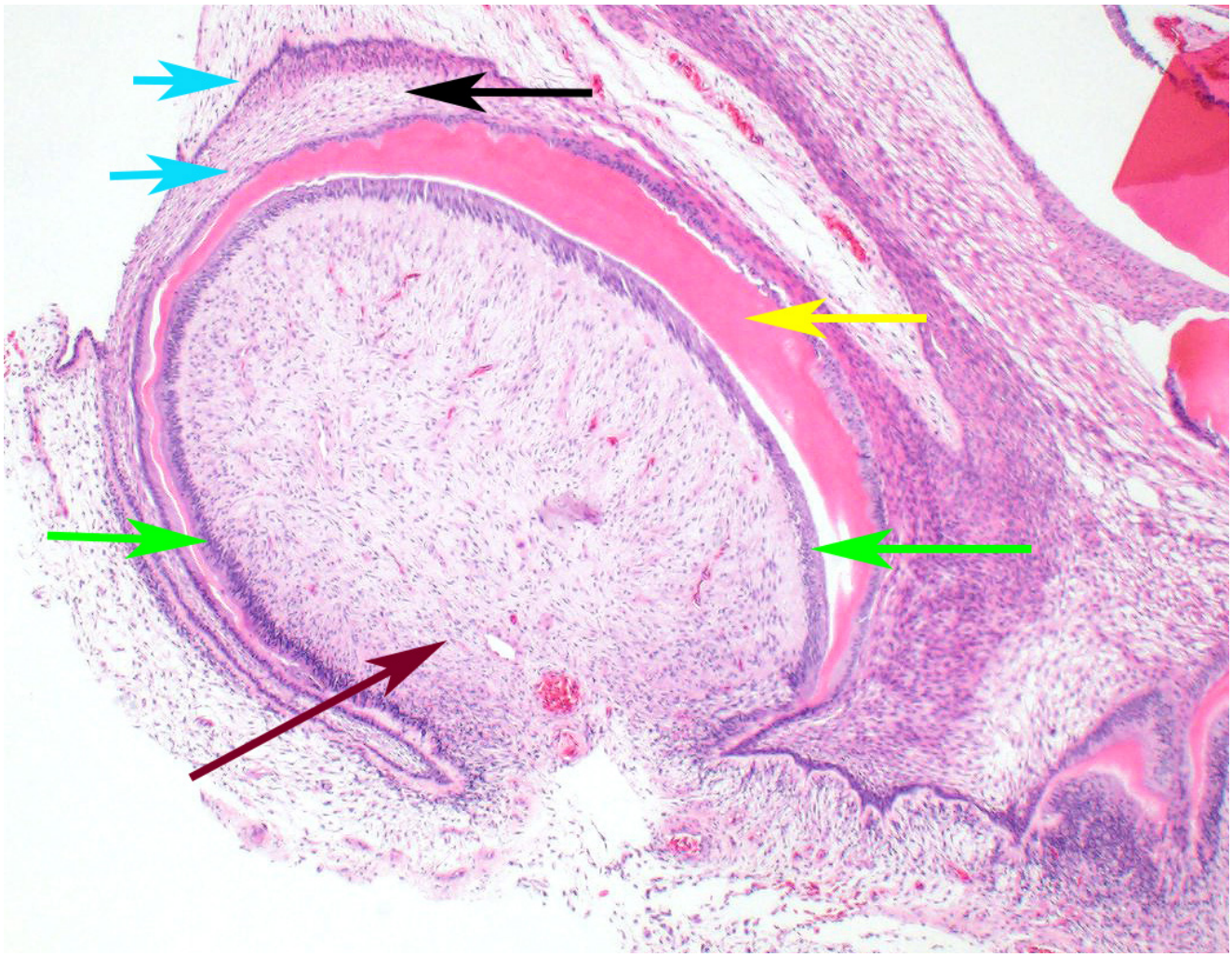
Oral mass, inner (palatine) left dental arcade: Ameloblastoma arising in an odontoma (previously odontoameloblastoma) with mucosal ulceration and proliferative new bone




***Maxilla boa. There are numerous attempts to recapitulate teeth throughout the mass, with variable combinations of ameloblasts, stellate reticulum, tubular dentin, odontoblasts, and mesenchyme resembling dental pulp. (HE 54X)***

**Contributor's Comment:** Histologic evaluation of the oral mass revealed a mixed odontogenic tumor containing a neoplastic population of odontogenic epithelium (ameloblastoma) as well as a differentiated mesenchymal component and tooth-like structures (odontoma). The combination of these two findings was most consistent with an ameloblastoma arising in an odontoma (AAO) or odontoameloblastoma (OA), an uncommon odontogenic neoplasm in veterinary and human medicine. In the most recent (2017) WHO classification of head and neck tumors, the term odontoameloblastoma (or ameloblastic odontoma) was discussed.[7] The current consensus concluded that, due to the lack of evidence that these tumors begin or recur as odontoameloblastomas, and that they often recur as ameloblastomas, the term ameloblastoma arising in an odontoma (AAO) was more appropriate.

Odontoameloblastomas have been reported in domestic and non-domestic mammalian species, but to our knowledge have not been recognized in reptiles.[1,4,5,8,13] An ameloblastoma has been reported in a wild black rat snake, with a single mass on the mandible.[2] In humans, OA or AAO are often locally aggressive with behavior and prognosis similar to ameloblastomas. In the

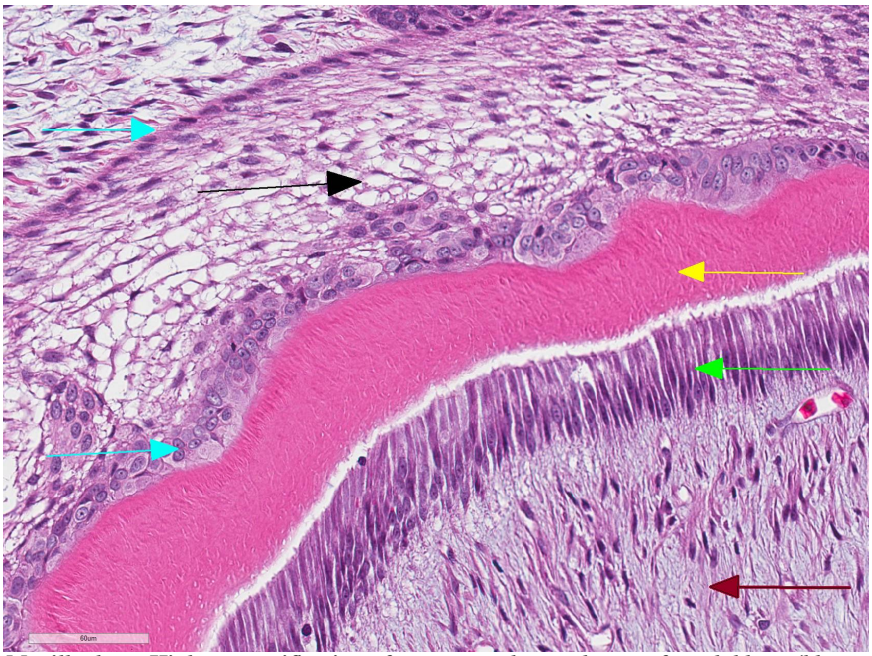


***Maxilla, boa. In a particularly well-formed prototooth at the edge of one section, a rudimentary enamel organ containing two layers of ameloblasts (blue arrows) separated by stellate reticulum-like tissue (black arrow), abuts a layer of dentin (yellow arrow), a layer of odontoblasts (green arrows), and surrounds vascular mesenchyme resembling dental pulp. (HE 40X)***

veterinary literature, odontoameloblastomas are similarly locally aggressive and expansile with destruction of the adjacent bone of the jaw. The mandible is a common site of the primary tumor, [1,4,5,8,13] though the lesion was maxillary in this case.

Diagnosis of an odontoameloblastoma relies on the presence of three components: neoplastic odontogenic epithelium, a mesenchymal component reminiscent of dental pulp, and dental matrix (dentin and enamel). Differentiation of an odontoameloblastoma or AAO from other mixed odontogenic tumors relies not only on the presence of these components but also the relative amount. Differentials such as an ameloblastic fibro-odontoma and ameloblastic fibroma should have a predominant ectomesenchyme (pulp stroma) component, and odontomas (both complex and compound), should have less odontogenic epithelium.

In this case, the mass did extend to the margins of the examined sections, and bony lysis was suspected on radiographs. However, no gross evidence of recurrence was noted at 4 months follow up.



***Maxilla, boa. Higher magnification of a prototooth., two layers of ameloblasts (blue arrows) are separated by stellate reticulum-like tissue (black arrow), abut a layer of dentin (yellow arrow), a layer of odontoblasts (green arrows), and surrounds vascular mesenchyme resembling dental pulp. (HE, 380X)***

**Contributing Institution:**

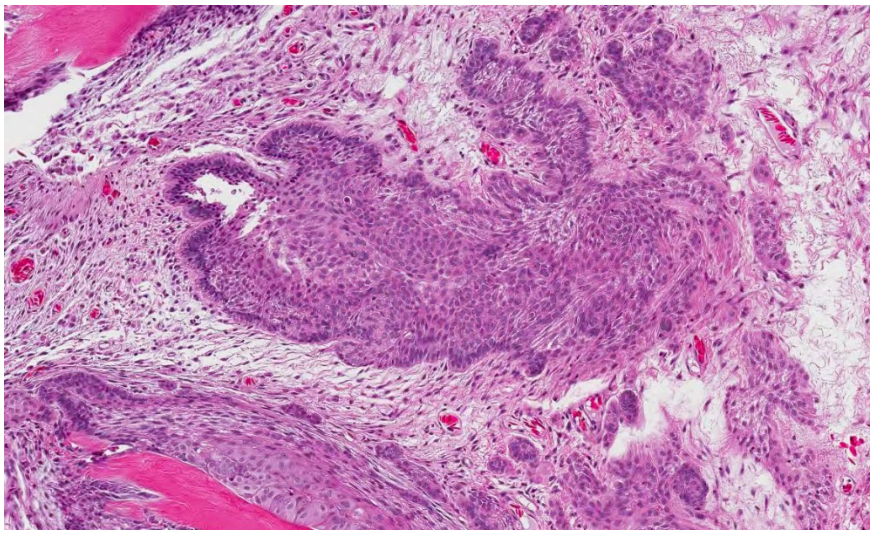
Wildlife Conservation Society
2300 Southern Blvd.
Bronx, NY 10460
https://www.wcs.org/

**JPC Diagnosis:** Gingiva and alveolar bone: Compound odontoma.

**JPC Comment**: This case is an excellent example of the difficulties of subclassifying odontogenic neoplasms, especially those in exotic species. While attendees had no problem identifying odontogenic epithelium and mineralized dental matrix, the issue of differentiating ectomesenchyme of the dental papilla from the surround loose fibrous stroma of the neoplasm, especially in a reptile, proved to be a challenge.

While careful consideration was given to the contributor's diagnosis of odontoameloblastoma, we prefer a very slightly altered diagnosis of odontoma. While we agree that this is a neoplasm composed of odontogenic epithelium, dental hard substance, and ectomesenchyme, in the sections we examined, we could not identify an overwhelming odontogenic epithelial proliferation to make the diagnosis of OA. The diagnosis of OA requires a greater proportion of odontogenic epithelium than in odontoma. In this case, the odontogenic epithelium was generally associated with prototeeth (i.e. well-formed denticles), as is seen in odontomas. While there are some areas of the tumor in which sheets of odontogenic epithelium are present without the formation of dental matrix or any apparent inductive effect on the surrounding mesenchyme, the majority of the neoplasm is composed of areas in which these three components are clearly represented.

Odontogenic neoplasms have been rarely reported in snakes, with a single previous report of ameloblastoma in a wild black rat snake (*Pantherophis alleghanensis)*[2] and a peripheral odontogenic fibromyxoma in a red tail boa (*Boa constrictor constrictor)* co-infected with arenavirus (inclusions were



***Maxilla, boa. In some areas, sheets of odontogenic epithelium, lacking any mineralized matrix or inductive effect, infiltrate the stroma. (Photo courtesy of: Wildlife Conservation Society, 2300 Southern Blvd., Bronx, NY 10460, https://www.wcs.org/)***

not seen in the neoplastic cells, unfortunately.)[7]

Snakes, like most reptiles (with the exception of some lacertids to include bearded dragons), fish, and amphibians are polyphydont, with continuous tooth renewal as opposed to humans, which are diphyodont, or monophyodont animals with continuously growing teeth (i.e, mice.) In polyphyodon models, teeth are not regenerated following tooth loss, but are continually developed under a highly complex and coordinated process including a number of important genes and gene products to include sonic hedgehog and Wnt/b-catenin. Those readers interested in this process are referred to references 6 and 9.

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**CASE IV:** AR17-0027-7 DVD (JPC 4117660).

**Signalment:** 4-month-old male prairie vole (*Microtus ochrogaster*)

**History:** On the day of necropsy, this animal was found hunched, and had dried blood around the anus and on the feces. Euthanasia via C02 and cervical dislocation was performed due to poor prognosis.

**Gross Pathology**: The roots of both first mandibular molars extended ventrally (2x2x1 mm) beyond the body of the mandible, and had blackened tips. The roots of both of the second mandibular molars extended from the body of the mandible, curling laterally and dorsally (3x2x1 mm). The tooth roots of maxillary molars 2 and 3 extended through the skull and into the ventral cranial vault, in the area of the pituitary gland, with the cranial pair extending in 1x1x1 mm and the caudal pair, 3x2x2 mm. An intussusception was present involving the ansa spiralis coli and proximal colon.

**Laboratory results:** NA.

**Microscopic Description:**

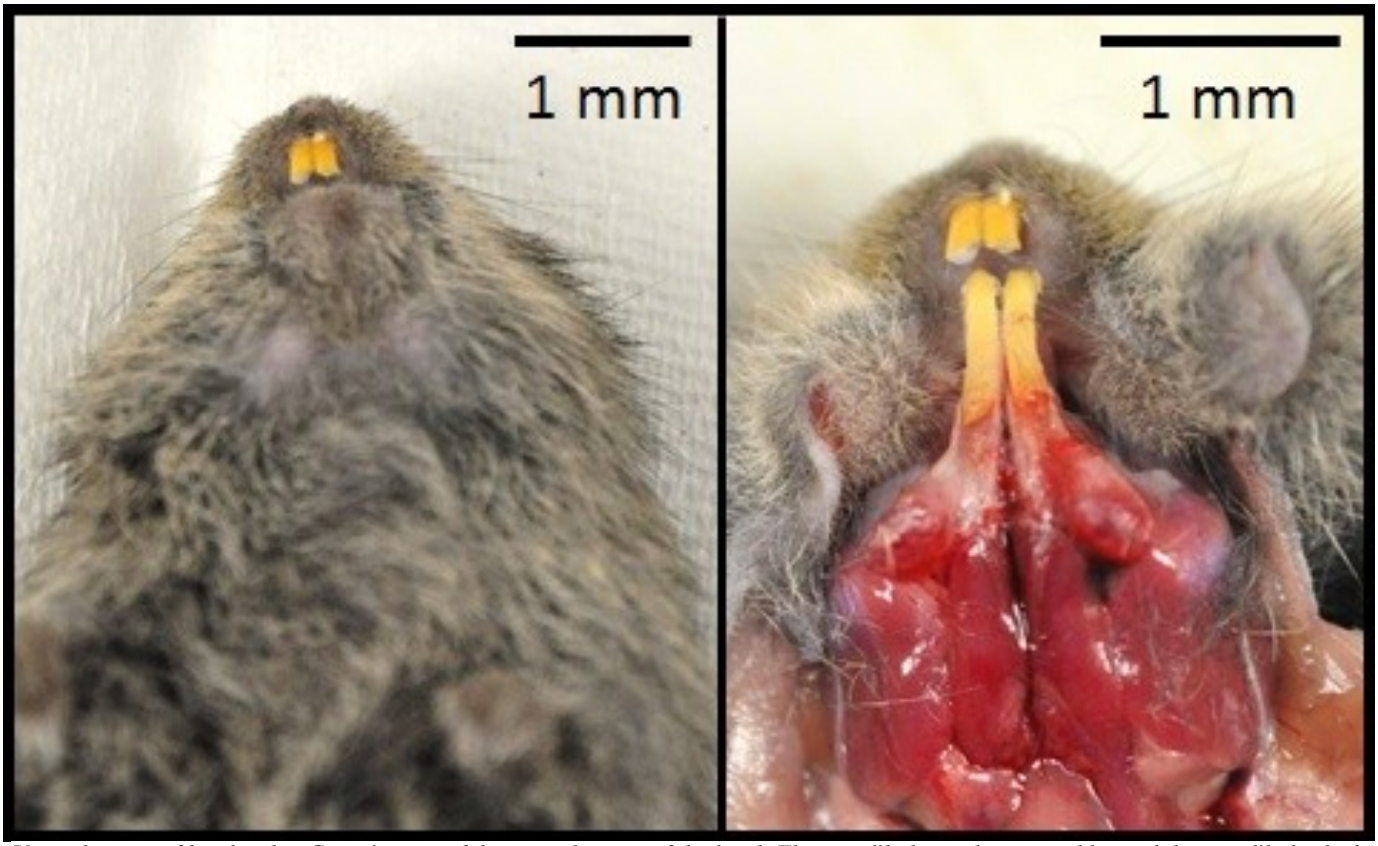
Sagittal section of the skull: The molar roots extend cranially, the first molar (M1) compresses the nasal sinuses, and the second and third molars (M2 and M3) extend into the cranial vault. The pulp cavities and dentin have irregularly scalloped edges, and the stellate reticulum is retained. The cortical bone overlying the molars is thin, irregularly scalloped, and has many smooth (resting) and haphazard (reversal) basophilic lines throughout. The bone is lined by closely spaced osteoblasts and fewer osteoclasts in Howship's lacunae, and some osteocytes are pale without cellular detail, or are not present in lacunae (necrosis).

**Contributor's Morphologic Diagnosis:**

Dental dysplasia with invasion of the cranium, maxillary molars

Degeneration and regeneration, multifocal, chronic, moderate, maxilla

**Contributor's Comment:** This animal was one of sixteen cases of laboratory prairie voles (*Microtus ochrogaster*) at our facility which presented with varying degrees of molar apical elongation in the mandible and/or maxilla. The animals ranged from 4 to 13 months old, and both genders were represented. All cases had bilateral mandibular molar roots that extended apically beyond the body of the mandible, and fourteen voles had maxillary molars which extended apically through the skull into the cranial vault and compressed the nasal sinuses. The histologic findings for all of these animals revealed dental dysplasia

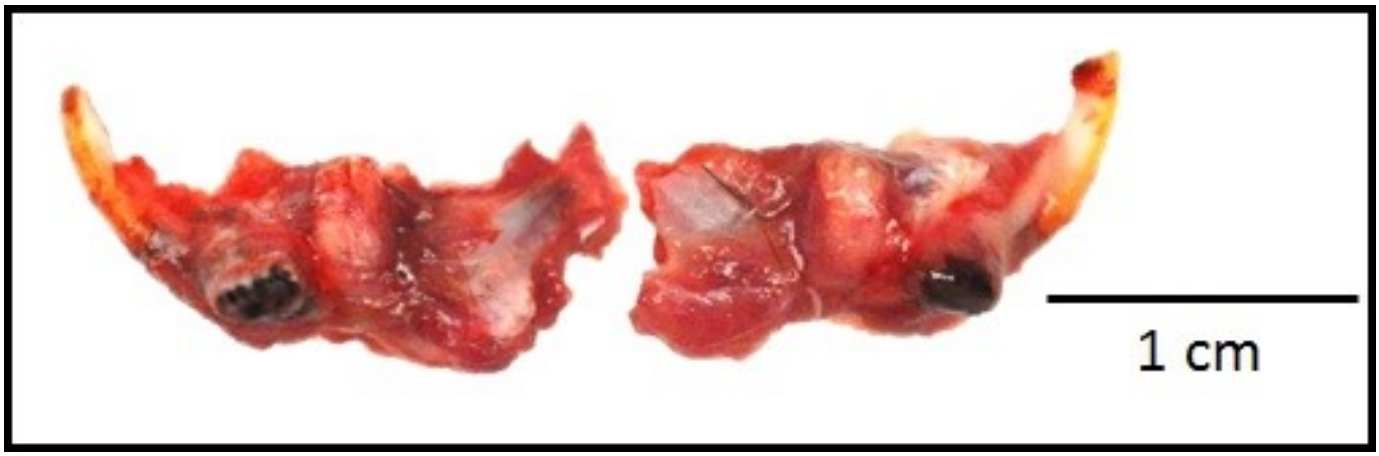



***Ventral aspect of head, vole: Gross images of the ventral aspect of the head: The mandibular molars extend beyond the mandibular body. (Photo courtesy of: Department of Comparative Medicine, Wake Forest School of Medicine, 1 Medical Center Boulevard, Winston-Salem, NC 27157)***

with abnormal dentin, irregular pulp cavities, and marked remodeling of the surrounding bone.

There was neither apparent correlation between age and the size of the mandibular root protuberances, nor between the size and any clinical sign. Six prairie voles had oral lesions (abscessation, food impaction, ulceration, osteomyelitis) which were attributed to the dental deformity, three had concurrent coronal incisor overgrowth, and two died of sepsis secondary to oral infection. The brain was unaffected in all but three cases where cerebral compression was noted.

Prairie voles have aradicular hypsodont dentition[10], which displays continual growth of teeth throughout life, offsetting the wear incurred from a fibrous diet. Other terms for this pattern of growth are hypselodont or elodont dentition.[8] Unlike other rodents including mice (*Mus musculus*) which have only continual growth of the incisors, all vole teeth, including the one incisor and three molars in each quadrant, continually grow. Other animals with complete aradicular hypsodont dentition include rabbits, guinea pigs, and chinchillas.[12] It has been proposed that the persistence of the stellate reticulum plays a role in the perpetual tooth growth in the incisors of mice and vole teeth.[8] The stellate reticulum is a stem cell niche within the cervical loop of the proximal tooth which sits between the inner and outer enamel epithelia.[9] Epithelial

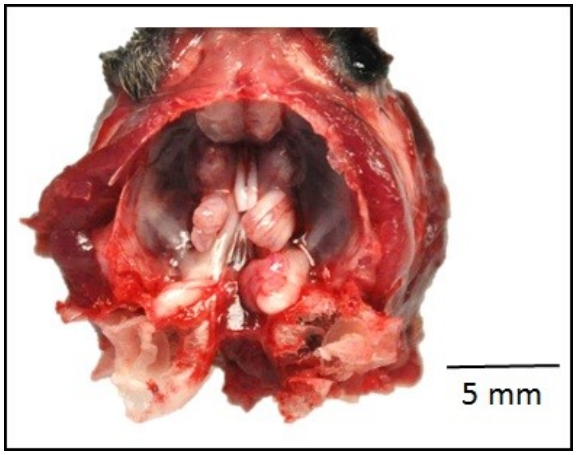



***Mandibles, vole:** The roots of the first and second mandibular molars extend beyond the body of the mandible. The first mandibular molars have blackened tips, and the second mandibular molars curl laterally and dorsally. (Photo courtesy of: Department of Comparative Medicine, Wake Forest School of Medicine, 1 Medical Center Boulevard, Winston-Salem, NC 27157)*

stem cells are thought to be located within the stellate reticulum and enamel epithelium (also known as Hertwig's epithelial root sheath) at the edge of the cervical loop. Stellate reticulum stem cells migrate to the inner enamel epithelium and support proliferating cells which then relocate distally to differentiate into ameloblasts.[14] In mice, the stellate reticulum of the molars regresses during maturation, explaining the cessation of growth. The regulation of growth in mouse incisors and the molars of sibling voles (*Microtus rossaiemeridionalis*) have been shown to be under the influence of FGF10, *Sox*2+ and Notch signaling, in addition to potential influence of BMP4.[2,14] The histology presented from this case showed retention of the stellate reticulum in the maxillary molars of an adult vole with dental dysplasia. Normal teeth from unaffected adult animals in this cohort also had retained stellate reticulum.

Similar findings in a colony of prairie voles at another facility have been studied, and it was speculated that a spontaneous mutation in dental stem cell regulatory genes was responsible for the condition. The inheritance was considered to be complex, as experimental inbreeding of affected animals produced no gross molar changes in the F2 offspring by 8-12 months of age.[8] In both this study and observations from our cases some animals were lethargic, moribund, or found dead, which was thought to have been attributable to the invasion of the skull and compression of the brain, although a definitive link could not be established.

A number of *Microtus* species (including *M. californicus californicus, M californicus vallicola, M. montanus, M. pennsylvanicus,* and *M. socialis*) have been reported with this abnormality[4]. Molar apical elongation in a colony of captive Amargosa voles (*Microtus californicus scirpensis*) was attributed to clinical signs including abnormal mentation, ocular discharge and abnormal mastication. Histology of these lesions showed variable hyperplasia, dysplasia, and atrophy of the inner and outer enamel epithelial layers.[4] A Japanese field vole (*Microtus montebelli*) from one study presented with maxillary molar macrodontia that protruded apically and invaded the brain as deep as the




***Ventral cranium: The tooth roots of maxillary molars 2 and 3 extend into the cranial vault. (Photo courtesy of: Department of Comparative Medicine, Wake Forest School of Medicine, 1 Medical Center Boulevard, Winston-Salem, NC 27157)***

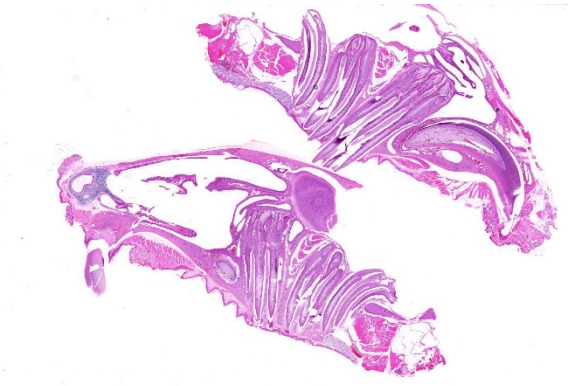
thalamic nuclei.[13] Coronal molar overgrowth without incisor abnormalities has been reported in a colony of laboratory pine voles (*Microtus pinetorum*). Changes in the husbandry of the pine vole colony, which included increasing dietary roughage and adding hard wood as enrichment, appeared to prevent further occurrence of this lesion.[3]

Although the stellate reticulum was also retained in the incisors of the adult voles in our cases, none of the incisors displayed apical elongation. This suggests that the cause of the dysplasia is more complex than simply a mutation in the stellate reticulum, or perhaps the incisor and molar stem cell niches are dissimilar. Another supposition is the possibility that a causative mutation may only affect the molar-specific mechanic and transduction pathway, or there may be differences in the periodontal ligament anchorage between incisors and molars.[8] Some studies have suggested that the cause of molar apical elongation is multifactorial, including genetic predisposition, deficient occlusal attrition and environmental factors such as inadequate roughage in the diet.[4]

A colony of Steppe lemmings (*Lagurus lagurus*), which are aradicular hypsodonts in the same subfamily as voles, had apical odontogenic dysplasia of the mandibular and maxillary molars with cranial vault invasion. In contrast, on histology, the apical overgrowths were composed of highly disorganized mature odontogenic structures, and more closely resembled hamartomas, which in aradicular hypsodonts have been termed elodontomas[5].Changes comparable to molar apical elongation and elodontoma formation occur in many aradicular hypsodont animals, including rabbits, squirrels, and degus.[1,6,7] These findings indicate that some degree of apical molar overgrowth is intrinsic in species with this dentition.[4]

**Contributing Institution:**

Wake Forest School of Medicine
Department of Pathology, Section on Comparative Medicine



***Sagittal section of head, vole. Two sagittal section of the head are presented for evaluation. There is marked elongation of the cheek teeth in both sections and they protrude into the overlying maxillary sinus. (HE, 5X)***

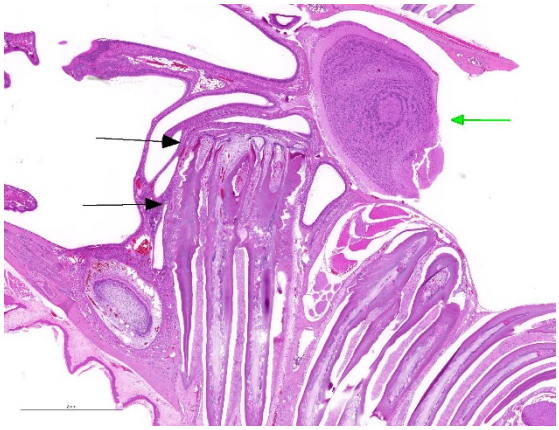
Medical Center Boulevard, Winston-Salem, NC 27157
www.wakehealth.edu

**JPC Diagnosis:** Head, sagittal section, cheek teeth: Odontogenic dysplasia with alveolar bone remodeling, and penetration of the maxillary sinus and calvarium.

**JPC Comment**: The contributor has given us an excellent review of dental growth in rodents as well as the available literature on dysplastic teeth lesions in the rodent. Hyperplasia and dysplasia with apical elongation appears to be a considerable problem in voles of the genus *Microtus*. The changes noted in this particular case are similar to those which were well-described in a captive colony of Amargosa voles (*Microtus californicus scirpensis*) by Imai et al.[4]

In these particular voles the lesion of molar apical elongation (MAE) was characterized by a combination of hyperplasia and to a lesser extent dysplasia which was seen in 63% of the colony. The single predisposing factor in this particular report was age. The authors believe the entity to be multifactorial as a result of a) the nature of continuous growth of hypsodont teeth, inadequate occlusal attrition, and c) a possible genetic inheritance.

That particular paper also describes, with excellent photomicrographs, many of the changes seen in this condition. While it has often been referred to as dentinal dysplasia in rodents, the disorganization of elements seen in true odontogenic dysplasia is not evident in this particular sample other than mild compression of the intercuspal loops and scalloping of the dentin, so we prefer the overall diagnosis of hyperplasia as described by Imai et al. than dysplasia in this particular 4-month-old individual. It might be true that this lesion might become more dysplastic over time as the animal matured.



***Sagittal section of head, vole. The molar apices (black arrows) have grown dorsally through the maxilla into the maxillary sinus, compressing the turbinate bones. The olfactory lobe (within the cranium) is highlighted by the green arrow. (HE, 16X)***

The term odontogenic dysplasia has been applied to a number of proliferative masses in rodents and lagomorphs over the years, and used interchangeably with odontoma, pseudo-odontoma, and elontoma (all of which incorrectly imply a neoplastic origin.) The etiology of these masses is likely to be disruption of the embryonic enamel organ by a variety of means, including irritation, microtrauma, or infection. It is characterized by a disorganized mass of odontogenic epithelium with significant mineralized dental matrix (dentin, enamel, and in the case of hypsodont teeth, cementum.)[11]

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