Odontoameloblastoma with extensive chondroid matrix deposition in a guinea pig

Hannah E. Wong,[1] Joanna Hedley, Nadene Stapleton, Brian Murphy, Simon L. Priestnall

Department of Pathobiology and Population Sciences, Royal Veterinary College, Hertfordshire, UK (Wong, Priestnall); Department of Clinical Sciences and Services, Royal Veterinary College, London, UK (Hedley, Stapleton); Department of Pathology, Microbiology, and Immunology, School of Veterinary Medicine, University of California–Davis, Davis, CA (Murphy).

[1]Corresponding author: Hannah E. Wong, Department of Pathobiology and Population Sciences, Royal Veterinary College, Hawkshead Lane, North Mymms, Hertfordshire AL9 7TA, UK.
hwong@rvc.ac.uk

Running title: Odontoameloblastoma with chondroid matrix in a guinea pig

Abstract. Odontoameloblastomas (previously incorporated within ameloblastic odontomas) are matrix-producing odontogenic mixed tumors and are closely related in histologic appearance to the 2 other types of matrix-producing odontogenic mixed tumors: odontomas and ameloblastic fibro-odontomas. The presence or absence of intralesional, induced non-neoplastic tissue must be accounted for in the diagnosis. Herein we describe a naturally occurring odontoameloblastoma with extensive chondroid cementum deposition in a guinea pig (*Cavia porcellus*). Microscopically, the mass featured palisading neoplastic odontogenic epithelium closely apposed to ribbons and rings of a pink dental matrix (dentinoid), alongside extensive sheets and aggregates of chondroid cementum. The final diagnosis was an odontoameloblastoma given the abundance of odontogenic epithelium in association with dentinoid but a paucity of pulp ectomesenchyme. Chondroid cementum is an expected anatomical feature of cavies, and its presence within the odontoameloblastoma was interpreted as a response of the ectomesenchyme of the dental follicle to the described neoplasm. Our case illustrates the inductive capabilities of odontoameloblastomas while highlighting species-specific anatomy that has resulted in a histologic appearance unique to cavies and provides imaging and histologic data to aid diagnosis of these challenging lesions.

Key words: Chondroid; guinea pigs; odontoameloblastoma; odontogenic mixed tumor.

Matrix-producing odontogenic mixed lesions are characterized by the presence of proliferative odontogenic epithelium in the presence of induced dental matrix material (dentin or enamel) and pulp ectomesenchyme. The lesions include odontoameloblastomas, odontomas (compound and complex), and ameloblastic fibro-odontomas. Both odontoameloblastomas and ameloblastic fibro-odontomas have been incorporated within the term ameloblastic odontoma.

Odontoameloblastomas are rare tumors that originate from odontogenic epithelium and, although they are not considered to be malignant as they do not metastasize, they frequently have extensive infiltrative local growth that destroys the surrounding bony tissues.[10] Complete surgical excision with wide margins is required for full resolution, and this can often be challenging to achieve given the anatomic location of these tumors. Odontoameloblastomas are characterized histologically by features of odontogenic epithelium, such as palisading of columnar epithelial cells with apical nuclei and basilar cytoplasmic clearing, and non-basilar epithelial cells connected by long intercellular bridges in combination with ectomesenchymal tissue and the production of dentin and possibly enamel.[17] Published reports of odontogenic tumors are rare in cavies, and those reports presented with supporting histologic evidence are restricted to 2 complex odontomas (synonym elodontoma)[6] and an ameloblastic fibroma,[25] all identified in domestic guinea pigs (cases were reviewed and their diagnosis, according to Munday et al.,[18] confirmed). Herein we describe an odontoameloblastoma with significant chondroid cementum deposition arising from the caudal right maxilla of a guinea pig.

A 4-y-old male intact guinea pig was presented to the Exotics Service, Beaumont Sainsbury Animal Hospital, Royal Veterinary College, London for further investigation of unilateral exophthalmos of the right eye. On presentation, the guinea pig was bright, alert, and in good body condition. The right eye protruded markedly and was accompanied by mild serous

ocular discharge. The left eye was grossly unremarkable. The intraocular pressure of both eyes was similar (11–13 mm Hg). There was no evidence of facial distortion or upper respiratory disease. Conscious oral examination was limited but unremarkable. Causes of exophthalmos in guinea pigs include orbital neoplasia, odontogenic abscesses, Harderian or lacrimal gland lesions, dental disease, orbital cellulitis or abscess, and trauma. Further testing were therefore recommended, but declined by the owner at this stage; supportive treatment of meloxicam (Metacam, Boehringer Ingelheim, Bracknell, Berkshire, UK) and enrofloxacin (Baytril, Bayer, Reading, Berkshire, UK) was continued. At re-examination 2 wk later, the guinea pig had lost 10% of its body weight and had severe right-sided exophthalmos.

Computed tomography imaging revealed an irregular exophytic mass originating from the caudal right maxilla, disrupting and effacing the orbitosphenoid bone and expanding into the right retrobulbar space (Fig. 1). The 12 × 14 mm mass was composed of mixed soft tissue attenuation and patchy mineralization. The mass displaced medially the last 2 maxillary cheek teeth on the right, and compressed the nasopharynx, resulting in partial stenosis. A mineralized chronic abscess or an ossifying tumor was suspected. Surgery was performed to remove the right eye and sample the mass. The retrobulbar space contained proliferative soft tissue, mineralized tissue, and purulent material. Material from the retrobulbar space was removed by curette, and the area was flushed with saline. Culture of sampled tissue resulted in growth of *Bacteroides* spp. and *Corynebacterium* spp. The guinea pig recovered well from the surgery and was discharged, and the antibiotics and analgesics were continued.

Tissue submitted for histologic examination included the globe, a piece of glandular tissue, and multiple small fragments of the mass. Tissues were fixed for 48 h, trimmed, and

embedded in paraffin; 5-µm thick sections were cut and stained with hematoxylin and eosin. Selected sections were additionally stained with Masson trichrome.

Re-examination of the guinea pig 6 mo post-surgery revealed substantial regrowth of the neoplasm. Dysphagia was reported by the owner. Soft tissue protruded from the right orbit, and a small amount of purulent material was expressed from the site. Skull radiographs confirmed extensive regrowth of the neoplasm to approximately half of the original size. The guinea pig was euthanized 2 wk later because of progressive dysphagia. Autopsy confirmed the presence of an irregular, exophytic, variably firm mass protruding into the right orbit that appeared to originate from the caudal right maxilla, but did not reveal any other significant lesions. Further samples of the mass and representative organs were submitted for routine histologic examination. There was no evidence of distant metastatic spread within the examined tissues.

The proliferative tissue submitted from the surgical biopsy was composed of a neoplasm, characterized by 3 principal histologic features: odontogenic epithelium, ribbons and rings of mineralized dental matrix (dentin), and extensive deposition of subepithelial sheets of chondroid cementum. The odontogenic epithelium was organized into sheets and broad interlinking trabeculae (Fig. 2). It demonstrated the cardinal odontogenic features of cuboidal-to-columnar epithelium palisading perpendicular to a basement membrane with apical nuclei and basilar cytoplasmic clearing, in combination with non-basilar epithelial cells with long intercellular bridges (Fig. 3). The non-basilar epithelial cells were fusiform, with a variable amount of eosinophilic cytoplasm (stellate reticulum–like architecture). Multifocally and occasionally the odontogenic epithelium aligned and palisaded along ribbons and rings of pink matrical material interpreted as dentin (Fig. 3). Extensive regions of the lesion were comprised of chondroid cementum (Figs. 2, 3). Within the population of neoplastic odontogenic epithelium, there was

minimal anisocytosis and anisokaryosis, and mitotic figures were not observed. The proliferative tissue collected at autopsy from the right orbit and caudal maxilla had the same histologic features as the tissue submitted from the surgical biopsy.

The glandular tissue was diffusely infiltrated and partially effaced by large numbers of degenerate neutrophils and eosinophilic cell debris surrounded by fibroplasia. The gland was presumed to be Harderian gland given the tissue's anatomic location and histologic appearance. The cause of the chronic suppurative adenitis was not identifiable on the examined sections, and there was no evidence of neoplastic tissue within the gland. We concluded that the adenitis was the result of disruption of the area by the odontogenic neoplasm, presumptively as a result of pressure necrosis. Examination of the globe revealed marked ulcerative keratitis presumed to be secondary to exophthalmos.

Examination of the histologic features of our case revealed neoplastic odontogenic epithelium, confirming the presence of an odontogenic neoplasm, which was further classified as a mixed/inductive tumor given the association with mineralized dental matrix. In animals, 4 forms of inductive odontogenic lesions associated with dental matrix deposition are recognized: ameloblastic fibro-odontoma, odontoma (complex and compound), odontoameloblastoma, and infiltrative inductive ameloblastic fibromas (a pan-species term that includes feline inductive odontogenic tumors).[18] Some investigators consider odontomas, and compound odontomas in particular, to represent hamartomas as opposed to true neoplasms.

We favor the diagnosis of odontoameloblastoma because of the relative abundance of neoplastic odontogenic epithelium and relative disorganization of the mineralized dentinoid. The presence of chondroid matrix is unique to this lesion and is interpreted as a response of the

125 residual ectomesenchyme of the dental follicle to the neoplastic odontogenic epithelium. Cavies
126 produce chondroid cementum, which is analogous to cementum in other species.[13]
127 Sequential reviews of veterinary histology and terminology have resulted in
128 reclassification of whole or part of previously recognized entities.[23] The permeation of these
129 reclassifications across the literature has varied, resulting in multiple synonyms or, more
130 challengingly, conflicting classifications of lesions depending on the classification scheme used.
131 Terms that have been used or are in use in human or veterinary pathology for lesions
132 described as odontoameloblastoma in our paper include: odontogenic ameloblastoma,
133 ameloblastic odontoma, odontoblastoma, ameloblastic fibro-odontoma, odontoma
134 multidentiferum proliferans, and mixed odontogenic tumor.[9,20] In domestic animal pathology,
135 use of the terms odontoameloblastoma and ameloblastic odontoma have been and remain
136 prevalent to describe an ameloblastoma with foci of dentin or enamel.[10,28] However, a review of
137 canine and feline odontogenic tumors published in 1992[21] highlighted that the veterinary term
138 "ameloblastic odontoma" encompassed both ameloblastic fibro-odontomas and
139 odontoameloblastomas; entities that had been subdivided in human oral pathology. The authors
140 opined that the low incidence of these neoplasms in veterinary medicine did not warrant the use
141 of the additional subdivisions and that the term ameloblastic odontoma was sufficient. However,
142 a different veterinary review published in the same year[10] favored that subdivision because of the
143 difference in clinical behavior between odontoameloblastomas and ameloblastic odontomas
144 given that odontoameloblastomas are associated with local invasion, bone lysis, and the potential
145 for recurrence, whereas ameloblastic fibro-odontomas are noninvasive and rarely recur.[10,16]
146 A consensus regarding this specific issue within the nomenclature has not been reached.
147 The term ameloblastic odontoma is still in use,[15,24] but is described as obsolete elsewhere.[2,5] To

148 complicate matters further, ameloblastic odontoma is frequently considered to be a synonym of
149 odontoameloblastoma.[17] This is problematic because, although the term ameloblastic odontoma
150 may include cases classified as odontoameloblastomas, it also included or still includes cases of
151 ameloblastic fibro-odontomas. A review of veterinary odontogenic tumors that reclassified
152 historical cases according to the World Health Organization human classification system[1]
153 described cases of ameloblastic fibro-odontomas originally classified as ameloblastic
154 odontomas.[2] The review emphasized that any change of nomenclature applied to previously
155 published cases required review of the histologic features of each lesion before reclassification to
156 ensure that diagnostic subtleties are not lost.

157 Our review of 2 published cases using the term ameloblastic odontoma revealed a
158 suspected odontoameloblastoma in a llama[24] and an ameloblastic fibro-odontoma in a rat.[15] The
159 histologic features of an ameloblastic odontoma associated with the mandibular incisor teeth of a
160 llama described in the paper were proliferating ameloblasts in the presence of dentin. These are
161 features suggestive of an odontoameloblastoma; however, there are no histologic images
162 available upon which to conclusively review the diagnosis.[24] On assessment of the histologic
163 images, the ameloblastic odontoma described in a Sprague–Dawley rat has an apparent
164 abundance of ectomesenchymal stroma (pulp) relative to odontogenic epithelium,[15] therefore we
165 would reclassify this lesion as an ameloblastic fibro-odontoma rather than an
166 odontoameloblastoma using the classification scheme that we applied to our case.[18] However
167 reclassification of other investigators' published works is perilous, given that the entire specimen
168 is typically not available for examination.

Species with published odontogenic tumors that had appropriate histologic descriptions and images for review to confirm the diagnosis of odontoameloblastoma include non-human primates,[29] rat,[19] sheep,[7] cow,[8] horse,[19] cat,[22] and dog.[27]

A spontaneous ameloblastic fibroma has been reported in a young guinea pig.[25] These tumors are derived from odontogenic epithelium and pulpal mesenchyme. Ameloblastic fibromas are rare in all species, but are most commonly found in young cattle.[11] Ameloblastic fibro-odontomas are similar to ameloblastic fibromas, but contain more advanced dentinal differentiation, with production of dentin and possibly enamel matrices. A complex odontoma is formed of fully differentiated dental components, but an absence of tooth-like structures, which is in contrast to a compound odontoma in which the fully differentiated dental components form tooth-like structures referred to as "denticles." The term elodontoma was defined for odontoma-like lesions in species with continuously erupting (elodont) teeth, and it was originally applied to lesions observed in tree squirrels (*Paraxerus cepapi*).[3] This term has subsequently also been used to describe odontoma-like lesions in guinea pigs.[6] These tumor-like lesions are currently understood to arise subsequent to odontogenic dysplasia caused by inflammation, trauma, toxicosis, or age.[14] In our case, the relative abundance of neoplastic odontogenic epithelium and relative disorganization of the dentinoid and chondroid cementum supported a diagnosis of odontoameloblastoma over compound odontoma or ameloblastic fibro-odontoma.

The unique feature of our case is the presence of abundant chondroid matrix within an odontoameloblastoma. Guinea pigs have chondroid cementum,[13] therefore it is likely that the chondroid matrix observed in this neoplasm has arisen from the ectomesenchymal tissue of the dental follicle associated with the odontoameloblastoma. In contrast, in humans, chondroid tissue is thought to occur in dental masses as a result of chondroid metaplasia of pulpal or other

mesenchymal tissue.[12,26] In at least one case, chondroid metaplasia occurred within inflamed pulp tissue previously damaged by a carious lesion[12] and, following experimentally induced damage, dental pulp was shown to differentiate into chondrocytes and osteocyte-like cells that produce cartilage-like matrix and bone-like matrix, respectively.[4] An odontoameloblastoma should be considered as a differential diagnosis for an odontogenic neoplasm in a guinea pig, and chondroid cementum may be present as a species-specific response.

Acknowledgments

We thank the owner of the guinea pig in this case for consenting to the autopsy examination. We are also grateful for the expertise of the Royal Veterinary College (RVC) diagnostic imaging service and the RVC histology staff.

Declaration of conflicting interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

HE Wong is funded by the Wellcome Trust (RG63078). The Wellcome Trust had no involvement in the data collections or manuscript preparation.

References

1. Barnes L, et al., eds. World Health Organization classification of tumours. Pathology and genetics of head and neck tumours. Lyon, France: IARC Press, 2005.
2. Bell CM, Soukup JW. Nomenclature and classification of odontogenic tumors. Part II: clarification of specific nomenclature. J Vet Dent 2014;31:234–243.
3. Boy SC, Steenkamp G. Odontoma-like tumours of squirrel elodont incisors-elodontomas. J Comp Pathol 2006;135:56–61.

4. Braut A, et al. Analysis of the odontogenic and osteogenic potentials of dental pulp in vivo using a Col1a1-2.3-GFP transgene. Int J Develop Bio 2003;47:281–292.
5. Burrough ER, et al. Spontaneous odontoameloblastoma in a female Sprague Dawley rat. J Vet Diagn Invest 2010;22:998–1001.
6. Capello V, et al. Elodontoma in two guinea pigs. J Vet Dent 2015;32:111–119.
7. Dubielzig RR, Griffith JW. An odontoameloblastoma in an adult sheep. Vet Pathol 1982;19:318–320.
8. Elvio L, et al. Odontoameloblastoma in a calf. J Vet Dent 2013;30:248–250.
9. Ernst H, Mohr U. Ameloblastic odontoma of the mandible, rat. In: Jones TC, et al., eds. Cardiovascular and Musculoskeletal Systems. Monographs on Pathology of Laboratory Animals (sponsored by the International Life Sciences Institute). Berlin: Springer, 1991:218–219.
10. Gardner DG. An orderly approach to the study of odontogenic tumours in animals. J Comp Pathol 1992;107;427–438.
11. Gardner DG. Ameloblastic fibromas and related tumours in cattle. J Oral Pathol Med 1996;25:119–124.
12. Giardino L, et al. Chondroid metaplasia in inflamed pulp tissue: a case report. Oral Surg, Oral Med, Oral Pathol, Oral Radiol Endod 2006;102:42–45.
13. Hall BK, Witten PE. Plasticity of and transitions between skeletal tissues in vertebrate evolution and development. In: Anderson JS, Sues H-D, eds. Major Transitions in Vertebrae Evolution. Bloomington, IN: Indiana University Press, 2006:13–56.
14. Head K, et al. Histological classification of tumors of odontogenic origin in domestic animals. In: Head K, ed. Histological classification of tumors of alimentary system in

238 domestic animals. 2nd series. (Vol. 10, World Health Organization international
239 classification of tumors of domestic animals). Washington, DC: Armed Forces Institute
240 of Pathology, 2003:46–57.
241 15. Li Y, et al. Spontaneous peripheral ameloblastic odontoma in a male Sprague-Dawley rat.
242 Toxicol Res 2017;33:141–147.
243 16. Mosqueda-Taylor A. Odontoameloblastoma. In: Barnes L, et al., eds. World Health
244 Organization Classification of Tumours. Pathology and Genetics of Head and Neck
245 Tumours. Lyon, France: IARC Press, 2005:312.
246 17. Mosqueda-Taylor A, et al. Odontoameloblastoma. Clinico-pathologic study of three cases
247 and critical review of the literature. Oral Oncol 2002;38:800–805.
248 18. Munday J, et al. Tumors of the alimentary tract. In: Meuten D, ed. Tumors of Domestic
249 Animals. 5th ed. Ames, IA: Wiley, 2017:530–544.
250 19. Murphy B, et al. Mandibular odontoameloblastoma in a rat and a horse. J Vet Diagn Invest
251 2017;29:536–540.
252 20. NCBI Resource Coordinators. MedGen UID 352814. Database resources of the National
253 Center for Biotechnology Information. Nucleic Acids Res 2016 4;44(D1):D7–19.
254 21. Poulet FM, et al. A survey of epithelial odontogenic tumors and cysts in dogs and cats. Vet
255 Pathol 1992;29:369–380.
256 22. Quigley PJ, Leedale AH. Tumours involving bone in the domestic cat: a review of fifty-eight
257 cases. Vet Pathol 1983;20:670–686.
258 23. Soukup JW, Bell CM. Nomenclature and classification of odontogenic tumors. Part I:
259 historical review. J Vet Dent 2014;31:228–232.
260 24. Step DL, et al. Ameloblastic odontoma in the mandible of a llama. Can Vet J 2003;44:824–

827.

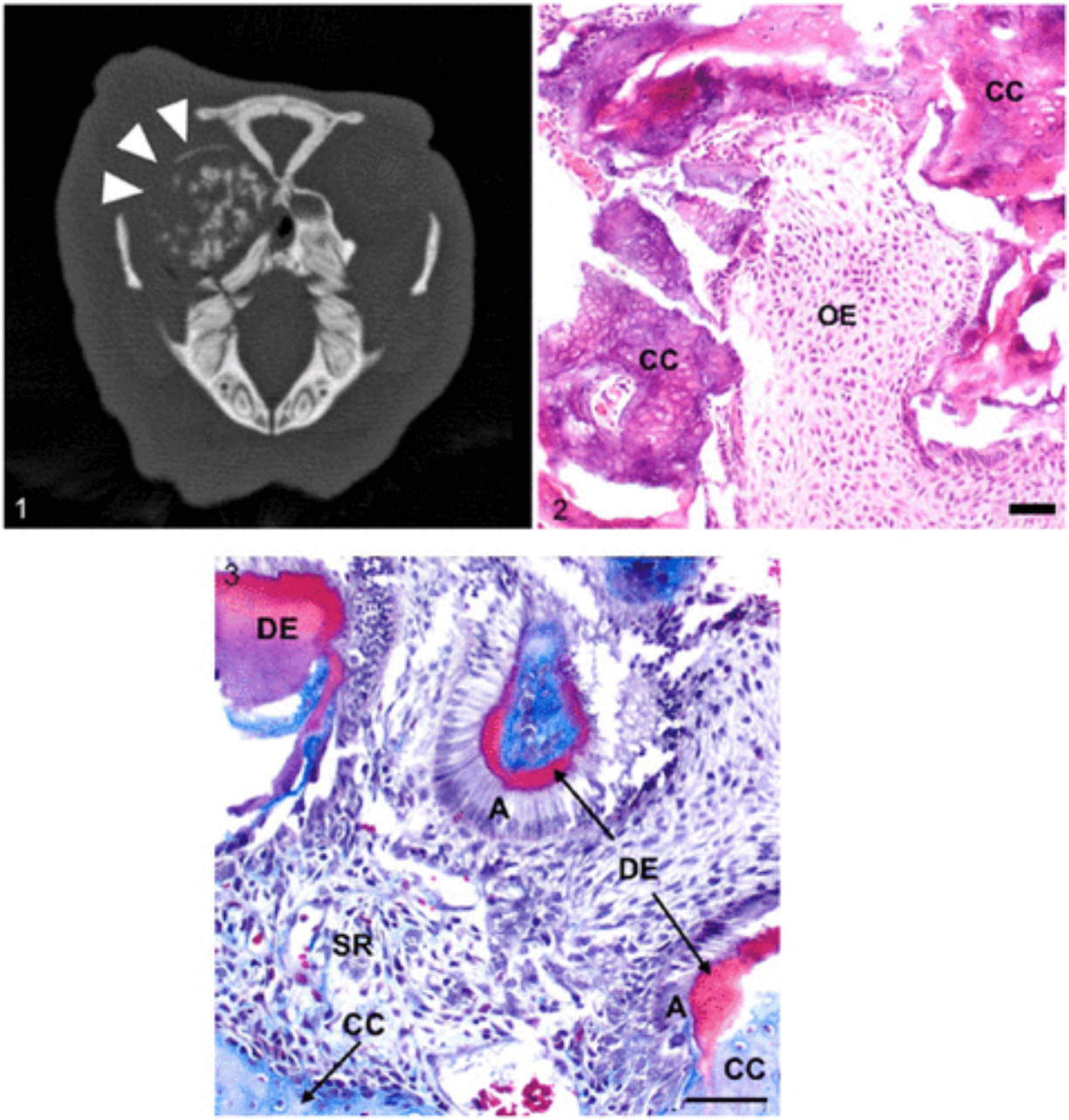
25. Tanaka M, Sawamoto O. Spontaneous ameloblastic fibroma in a young guinea pig. J Tox Pathol 2013;26:325–328.

26. Tenorio F, et al. Chondroid metaplasia in a fibroepithelial polyp of gingiva. J Clin Diagn Res 2016;10:9–10.

27. Verstraete FJM, et al. The histological nature of epulides in dogs. J Comp Pathol 1992;106:169–182.

28. Walsh KM, et al. Epithelial odontogenic tumours in domestic animals. J Comp Pathol 1987;97:503–521.

29. Yanai T, et al. Odontoameloblastoma in a Japanese monkey (*Macaca fuscata*). Vet Pathol 1995;32:57–59.



Figures 1–3. Odontoameloblastoma originating from the caudal aspect of the right maxilla with extensive chondroid cementum in a guinea pig (*Cavia porcellus*). **Figure 1.** Computed tomography still image of a transverse skull section showing an irregular, exophytic mass disrupting and effacing the orbitosphenoid bone and expanding into the right retrobulbar space (arrowheads). The mass displaced medially the last 2 maxillary cheek teeth on the right and compressed the nasopharynx, resulting in partial stenosis. **Figure 2.** Fragments of

neoplasm primarily comprised of sheets and broad interlinking trabeculae of odontogenic epithelium (OE) with abundant sheets and aggregates of chondroid cementum (CC). H&E. Bar = 50 μm.

Figure 3. The neoplastic odontogenic epithelium of the maxillary odontoameloblastoma exhibits single layers of palisading columnar-to-cuboidal epithelial cells with antibasilar nuclei (ameloblasts, A). The neoplastic odontogenic epithelium palisades along irregular ribbons of dental matrix (dentin, DE). Centrally, the epithelium has long intercellular junctions (stellate reticulum, SR) and is bordered by chondroid cementum (CC). Masson trichrome stain. Bar = 50 μm.

Supplementary Data 1. Computed tomography imaging of the skull of the guinea pig, which demonstrates the irregular, exophytic mass originating from the right caudal maxilla, disrupting and effacing the orbitosphenoid bone, and expanding into the right retrobulbar space (arrowheads). The mass displaced medially the last 2 maxillary cheek teeth on the right, and compressed the nasopharynx resulting in partial stenosis.