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1 **Odontoameloblastoma with extensive chondroid matrix deposition in a guinea pig**

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14 Running title: Odontoameloblastoma with chondroid matrix in a guinea pig

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

32

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

34

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

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

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

58 ocular discharge. The left eye was grossly unremarkable. The intraocular pressure of both eyes
59 was similar (11–13 mm Hg). There was no evidence of facial distortion or upper respiratory
60 disease. Conscious oral examination was limited but unremarkable. Causes of exophthalmos in
61 guinea pigs include orbital neoplasia, odontogenic abscesses, Harderian or lacrimal gland
62 lesions, dental disease, orbital cellulitis or abscess, and trauma. Further testing were therefore
63 recommended, but declined by the owner at this stage; supportive treatment of meloxicam
64 (Metacam, Boehringer Ingelheim, Bracknell, Berkshire, UK) and enrofloxacin (Baytril, Bayer,
65 Reading, Berkshire, UK) was continued. At re-examination 2 wk later, the guinea pig had lost
66 10% of its body weight and had severe right-sided exophthalmos.

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

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

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

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

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

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

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

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

122 We favor the diagnosis of odontoameloblastoma because of the relative abundance of
123 neoplastic odontogenic epithelium and relative disorganization of the mineralized dentinoid. The
124 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 1992²¹ 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 year¹⁰ 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 system¹
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 llama²⁴ 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.

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

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

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

192 mesenchymal tissue.^{12,26} In at least one case, chondroid metaplasia occurred within inflamed
193 pulp tissue previously damaged by a carious lesion¹² and, following experimentally induced
194 damage, dental pulp was shown to differentiate into chondrocytes and osteocyte-like cells that
195 produce cartilage-like matrix and bone-like matrix, respectively.⁴ An odontoameloblastoma
196 should be considered as a differential diagnosis for an odontogenic neoplasm in a guinea pig, and
197 chondroid cementum may be present as a species-specific response.

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202 **Declaration of conflicting interests**

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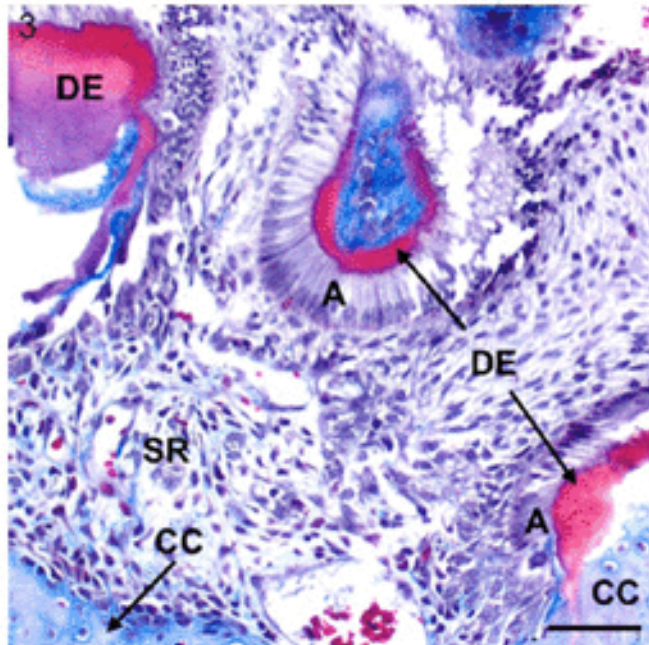
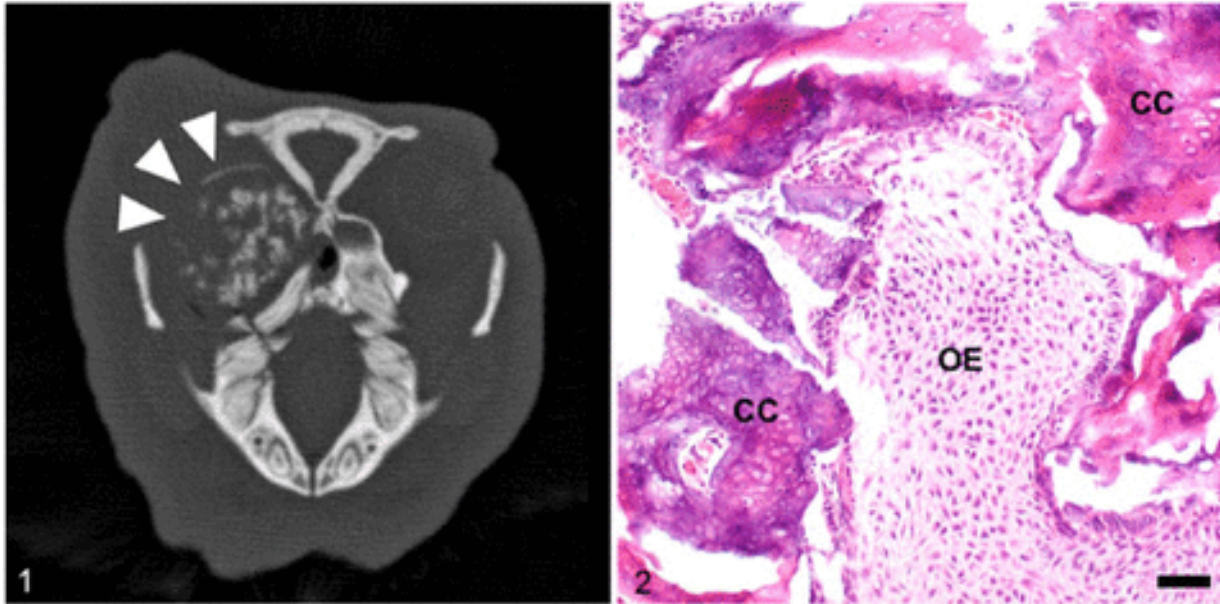
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- 272



273
 274 **Figures 1–3.** Odontoameloblastoma originating from the caudal aspect of the right maxilla with
 275 extensive chondroid cementum in a guinea pig (*Cavia porcellus*). **Figure 1.** Computed
 276 tomography still image of a transverse skull section showing an irregular, exophytic mass
 277 disrupting and effacing the orbitosphenoid bone and expanding into the right retrobulbar
 278 space (arrowheads). The mass displaced medially the last 2 maxillary cheek teeth on the right
 279 and compressed the nasopharynx, resulting in partial stenosis. **Figure 2.** Fragments of

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

283 **Figure 3.** The neoplastic odontogenic epithelium of the maxillary odontoameloblastoma exhibits
284 single layers of palisading columnar-to-cuboidal epithelial cells with antibasilar nuclei
285 (ameloblasts, A). The neoplastic odontogenic epithelium palisades along irregular ribbons of
286 dental matrix (dentin, DE). Centrally, the epithelium has long intercellular junctions (stellate
287 reticulum, SR) and is bordered by chondroid cementum (CC). Masson trichrome stain. Bar =
288 50 μ m.

289
290 **Supplementary Data 1.** Computed tomography imaging of the skull of the guinea pig, which
291 demonstrates the irregular, exophytic mass originating from the right caudal maxilla,
292 disrupting and effacing the orbitosphenoid bone, and expanding into the right retrobulbar
293 space (arrowheads). The mass displaced medially the last 2 maxillary cheek teeth on the right,
294 and compressed the nasopharynx resulting in partial stenosis.