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Ameloblastic carcinoma in horses: case report and literature review

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Abstract. Ameloblastic carcinoma is a malignant odontogenic neoplasm that has been reported only rarely in veterinary species. A 16-y-old Arabian crossbred mare was presented for evaluation of a hard mass on the body of the mandible, with evidence of osteolysis on radiographs. Incisional biopsies revealed an invasive neoplasm comprised of spindloid epithelial cells with a high mitotic count and partial dual cytokeratin–vimentin immunoreactivity. The horse was euthanized because of rapid tumor progression 3 mo after presentation. Postmortem evaluation revealed partial obliteration of the mandible by a large, firm-to-hard, tan, locally destructive and invasive mass with no gross or histologic evidence of metastasis. Postmortem histology revealed a poorly differentiated epithelial neoplasm with variably prominent features suggestive of odontogenic histogenesis: a plexiform ribbon architecture, infrequent basilar palisading with antibasilar nuclei, rare basilar cytoplasmic clearing, subepithelial matrix hyalinization, and partial dual cytokeratin–vimentin immunoreactivity. Features of malignancy included regions of necrosis, pronounced cellular atypia, a high mitotic count, extensive tissue invasion and local tissue destruction, and extension of neoplastic cells beyond the margins of the mandibular bone. Collectively, these features are most consistent with mandibular ameloblastic carcinoma. Including our case described here, ameloblastic carcinoma has been reported in only 5 horses. The microscopic features reported most consistently are dual cytokeratin–vimentin immunoreactivity, a high mitotic count, and basilar palisading. Ameloblastic carcinoma should be considered as a differential diagnosis for rapidly growing, locally invasive masses arising from the dentate jaw of horses.

Keywords: ameloblast; ameloblastic carcinoma; odontogenic neoplasm; odontogenesis; oral tumor; horses.

Among odontogenic neoplasms in veterinary species, odontogenic tumors without induction are diagnosed most commonly.[19] Included in this group are ameloblastoma, canine acanthomatous ameloblastoma, amyloid-producing ameloblastoma (also known as amyloid-producing odontogenic tumor), and ameloblastic carcinoma.[19] These non-inductive odontogenic neoplasms can generally be identified by the presence of 1 or more of the 4 cardinal features of odontogenic epithelium, including 1) palisading basal cells, 2) anti-basilar nuclei (reverse nuclear polarity), 3) basilar clear zone or vacuolation in the cytoplasm of the palisading basal cells, and 4) the presence of prominent desmosomal bridging and intercellular clear spaces in the center of epithelial islands (stellate reticulum-like cells).[19] These features are not universally present in all odontogenic lesions. Diagnostic features supportive of, but not specific for, odontogenic epithelial neoplasms are arrangement of epithelial cells in plexiform ribbons, "ink drop," or "medusoid" patterns; presence of loose, pale-pink, periodontal ligament-type supportive stroma; and dual immunoreactivity for cytokeratin and vimentin of neoplastic epithelial cells.[3,8,9,13,19] Additionally, the deposition of periepithelial hyalinized eosinophilic stroma (sometimes referred to by oral pathologists as Vickers–Gorlin effect) has been reported in ameloblastic neoplasms of human patients, and has been suggested to represent incomplete odontoblast induction with subsequent abortive dentin formation.[23,26] Although this feature can be seen with other epithelial tumors and is therefore not pathognomonic, in conjunction with other features listed above, it is considered to be supportive of ameloblastic histogenesis (Richard Jordan, pers. comm., 2020 Oct 24).

Ameloblastoma, the most common odontogenic neoplasm in horses, is locally aggressive and typically retains features of odontogenic epithelium.[19] According to the 2017 WHO classification of head and neck tumors, ameloblastic carcinoma maintains some of the histologic characteristics of ameloblastoma, but also exhibits features of malignancy including cellular pleomorphism, increased numbers of mitotic figures, abnormal mitotic figures, increased nuclear-to-cytoplasmic (N:C) ratio, nuclear hyperchromatism, and

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invasion beyond the basement membrane, including vascular and/or perineural invasion.[5,19] Ameloblastic carcinomas can maintain typical plexiform or follicular patterns seen with ameloblastoma, or can instead have sheets, nests, or broad trabecular organization of neoplastic ameloblasts.[5] In addition, ameloblastic carcinomas often have loss of orderly differentiation from peripheral basal cells to central stellate reticulum, and centers of neoplastic islands may be comprised of solid basaloid, acanthomatous, or spindloid cells with variable cystic degeneration and/or necrosis.[5] However, ameloblastic carcinoma is exceedingly rare, is reported uncommonly in humans,[5,21] and only a few cases have been reported in horses, dogs, and a rat.[3,4,8,10,11,14,17,22]

In addition to ameloblastoma, a primary differential diagnosis for ameloblastic carcinoma is oral squamous cell carcinoma. These 2 neoplasms can have considerable overlap in gross and histologic features, particularly in poorly differentiated squamous cell carcinomas that may have a spindloid phenotype and scant keratinization.[19] In these cases, identification of 1 or more odontogenic epithelial features, as well as dual expression of cytokeratin and vimentin, are key for distinguishing between these 2 neoplasms.[3,8,9,13,19]

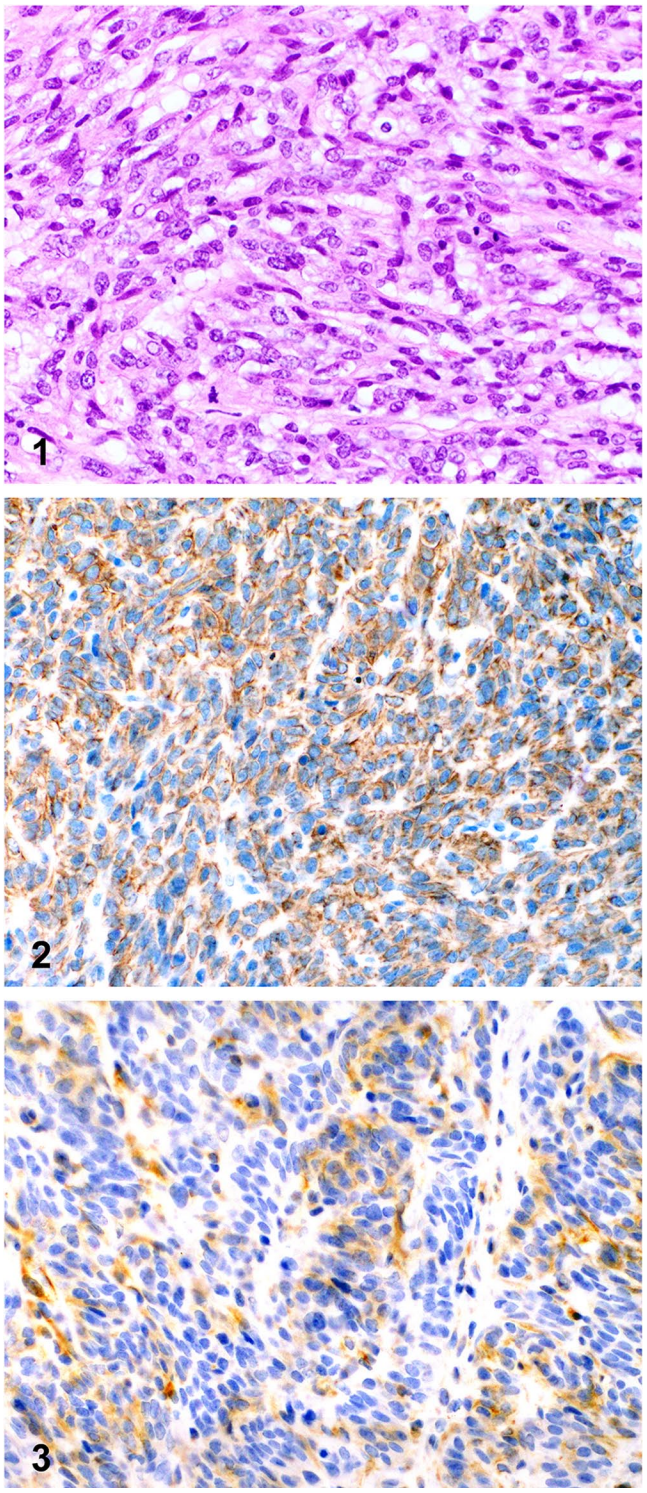
Only 4 cases of equine ameloblastic carcinoma are reported in the peer-reviewed literature,[3,4,14,22] and only 1 of these reports thoroughly details the gross and histologic features of an equine ameloblastic carcinoma.[3] Here we review features of published cases of equine ameloblastic carcinoma and describe the clinical progression, radiographic findings, and gross and histologic morphology of an ameloblastic carcinoma in a horse.

A 16-y-old Arabian crossbred mare initially was presented for assessment of a left mandibular mass that had been noticed 1 mo prior when it was <3 cm in diameter. On physical examination, a firm-to-hard, 4-cm diameter, round mass was identified on the ventrolateral aspect of the mid-left mandible (Suppl. Fig. 1). The patient was subclinical, and the remainder of the oral examination was unremarkable. Radiographs of the mass revealed loss of normal bone architecture surrounding teeth 307–308, with replacement by a discrete, raised, round, bony mass with a thin radiopaque outer wall and central multiloculated radiolucency surrounding tooth apices (Suppl. Fig. 2). Differential diagnoses were neoplasia, cyst, or tooth root abscess. Surgical exploration, which entailed incision and probing through the haired skin on the ventrolateral mandible, revealed a cystic mass surrounded by an outer firm-to-hard thin wall. During surgical exploration, multiple incisional biopsy samples were collected from the deep, central portion of the mass; these samples, which lacked overlying mucosa or skin, were submitted for histologic evaluation. Surgical resection was not performed.

Histologically, the mass was comprised of pleomorphic neoplastic epithelial cells that multifocally exhibited round, ovoid, cuboidal-to-short spindloid cell shapes, and were organized into islands, thin cords, and, in some areas, solid sheets. Neoplastic epithelial cells exhibited features of cytologic atypia, with scant cytoplasm, high N:C ratio, and variably hyperchromatic nuclei (Fig. 1). No mandibular or metaplastic bone was captured in the biopsy. At the time of biopsy submission, radiographic information was not available, and the mass was thought to be of haired skin origin, and a presumptive basal cell tumor was favored to explain the epithelioid and short spindle cell morphologies. However, upon radiograph review, this diagnosis seemed unlikely. The mass continued to progress and enlarge, and one month later, re-biopsy was pursued. Incisional biopsy samples included epidermis and underlying dermis to address a possible origin from haired skin structures. In this second biopsy, the neoplasm was determined to not be associated with the epidermis or dermal adnexa, but it did exhibit infiltrative growth into the subjacent stroma, which had not been identified in the original incisional biopsies. Given the infiltration of the neoplasm into surrounding tissue, as well as the numerous features of cytologic atypia, a diagnosis of carcinoma was made, with odontogenic, mucosal, or salivary gland tissues considered as epithelia of origin. Additionally, immunohistochemistry for cytokeratin and vimentin (Suppl. Table 1) revealed strong diffuse cytoplasmic cytokeratin immunoreactivity with weak-to-moderate cytoplasmic vimentin immunoreactivity in ~25% of the neoplastic epithelial cells (Figs. 2, 3). Given this partial dual immunoreactivity, odontogenic or salivary gland origins were favored.

Following the second biopsy submission, the neoplasm grew rapidly; the surgical incision site failed to heal fully, and the neoplasm exhibited robust column-like growth at the incision site, with a large, ulcerated portion of the neoplasm extending ventral to the mandible (Suppl. Fig. 1). Chemotherapy, radiation, and surgical excision were offered, but because of financial restrictions, the owner pursued palliative care, including oral piroxicam, topical medications (triamcinolone, dimethylsulfoxide, metronidazole), and bandaging for ulcer management. Three months following the initial presentation, the mass began to hemorrhage, the left mandibular lymph node became enlarged relative to the right, and the patient was inappetent and losing weight. Euthanasia was elected, and the patient was submitted for postmortem examination.

On gross postmortem examination, arising from the level of the mid-left mandible and effacing mandibular bone and surrounding soft tissues was an infiltrative and expansile, multilobulated, poorly demarcated, firm-to-hard mass (Fig. 4). The central portion of the mass, extending along the mandible from tooth 305 to tooth 310 (premolar and molar teeth), was $16 \times 9 \times 9$ cm, ovoid, pale-pink to tan, and had multifocal areas of necrosis. This portion of the mass displaced the mandible and associated teeth lingually within the mouth, resulting in occlusal trauma and ulceration of the mass and soft tissues by the maxillary premolar and molar teeth. Extending ventrally from the center of the mass and rupturing through the skin was a $15 \times 9 \times 7$ cm, exophytic,



Figures 1–3. Cytologic atypia and immunohistochemical features of an equine ameloblastic carcinoma. **Figure 1.** Neoplastic epithelial cells are poorly differentiated, with frequent spindloid morphology, hyperchromatic nuclei, a high N:C ratio, and a high mitotic count. H&E. **Figure 2.** Neoplastic cells have strong, diffuse, cytoplasmic immunolabeling for pan-cytokeratin. **Figure 3.** Neoplastic cells (~25%) have moderate-to-strong cytoplasmic immunolabeling for vimentin.

completely ulcerated, and hemorrhagic portion of the mass that was superficially colonized by myriad fly larvae. On the transverse cut surface, the mass was tan-white to pale-pink, multilobulated, and contained serpiginous aggregates of bony material that multifocally replaced portions of the mandible and individual teeth. Submandibular lymph nodes were diffusely and moderately enlarged (~6 × 4 × 3 cm) and dark purple-red, but maintained corticomedullary architecture on cut surface. Samples of the mass and lymph nodes were collected in 10% neutral-buffered formalin and processed routinely for histologic evaluation with H&E staining.

Histologically, the mass was comprised of an infiltrative and densely cellular epithelial population that was supported by a loose collagenous stroma, with features as described in the original biopsy specimen. Peripherally, this loose stroma merged with thin trabeculae of dense collagenous stroma that organized the neoplasm into lobules. At the lesion periphery, branching and anastomosing plexiform ribbons and cords (primitive dental lamina–like architecture) of neoplastic cells, 1–4 cells thick, infiltrated the adjacent stroma (Fig. 5). In some of these areas, the immediate periepithelial stroma was multifocally hyalinized pink-red with or without an accumulation of globular-to-linear eosinophilic material (Fig. 6). Infrequently, the neoplastic epithelial cells palisaded around islands of vascularized stroma. Rarely, small groups of palisading cells had antibasilar nuclei with basilar cytoplasmic clearing or vacuolation (reverse polarization; Fig. 7). There was no organized differentiation from the peripheral basal layer into the central stellate reticulum within the neoplastic islands; instead, within the center of lobules, neoplastic cells either maintained a spindloid shape or formed more solid aggregates of basaloid cells, and often had large, punctate, clear cytoplasmic vacuoles (vacuolar degeneration; Figs. 1, 7). There was no evidence of keratinization in the neoplastic population. The neoplastic cells had moderate anisocytosis and anisokaryosis, with 33 mitotic figures per ten 400× fields (total area 2.37 mm^2, ocular field number 22 mm). Multifocally, the neoplastic epithelium infiltrated into the adjacent alveolar bone and jaw. Surrounding the tumor were anastomosing thin trabeculae of proliferative and metaplastic bone covered by palisades of plump osteoblasts. Throughout the neoplasm were small foci of coagulative-to-lytic necrosis with accumulation of mild-to-moderate numbers of degenerate neutrophils and karyorrhectic nuclear debris. Within dense collagenous stroma trabeculae, there were mild accumulations of lymphocytes, plasma cells, and hemosiderin-laden macrophages. Histologic evaluation of the associated enlarged mandibular lymph node revealed lymphoid hyperplasia with no evidence of tumor metastasis. The concurrent presence of features consistent with odontogenic histogenesis, along with cytologic and clinical features of malignancy, informed a diagnosis of ameloblastic carcinoma.

Differential diagnoses considered included ameloblastoma and squamous cell carcinoma. Ameloblastoma is the

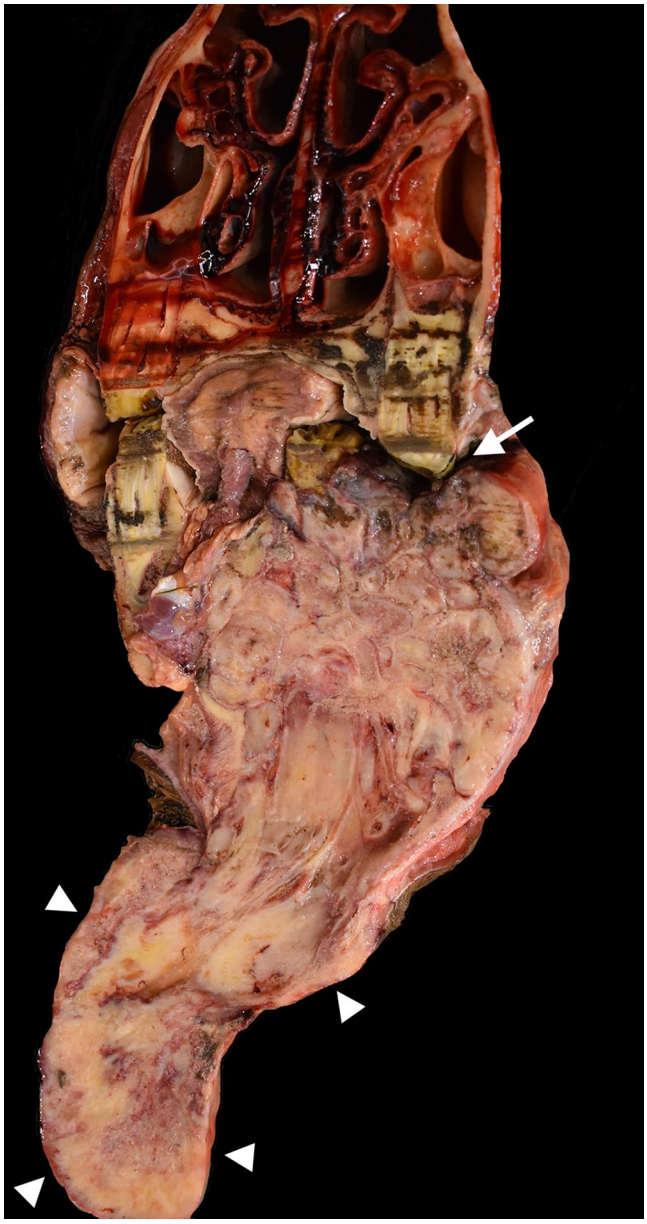
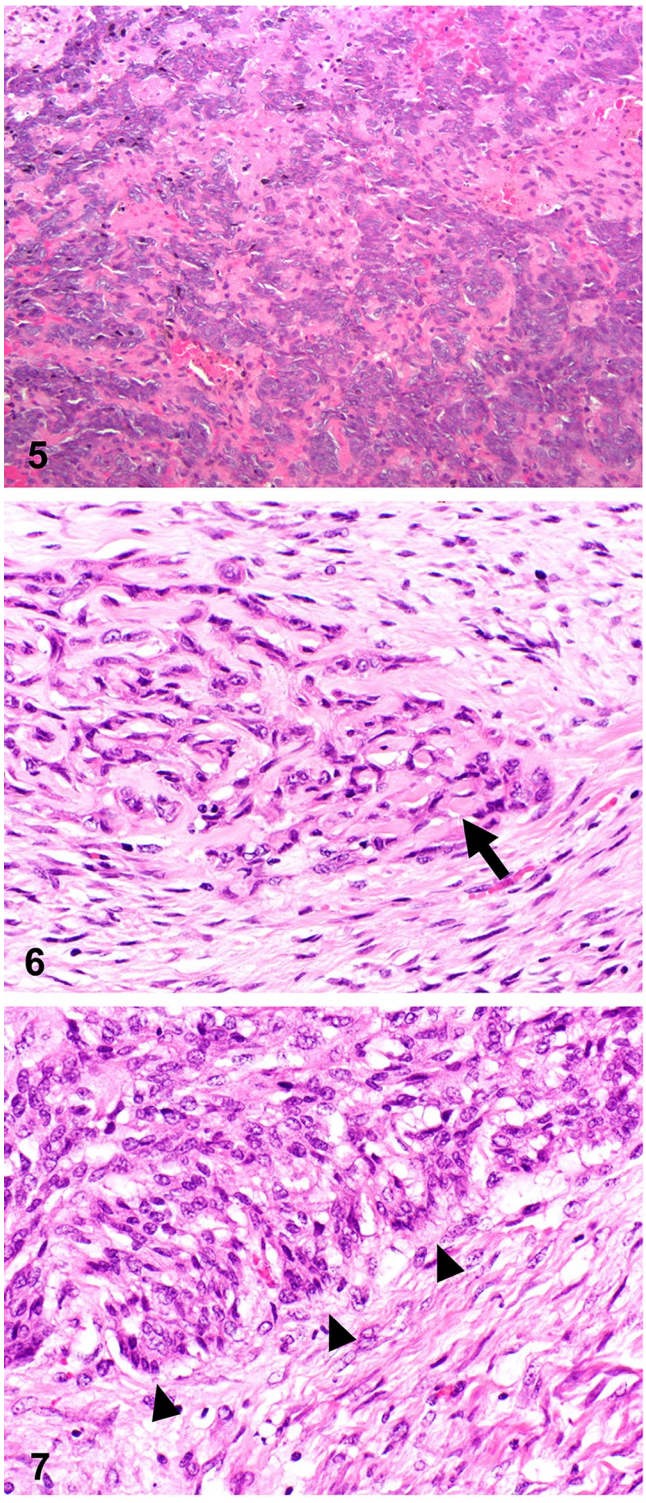


Figure 4. Gross features of an equine ameloblastic carcinoma. On transverse section of the head, a poorly demarcated, infiltrative and expansile, multilobulated mass replaces the left mandible, resulting in medial displacement of the mandibular premolar and molar teeth, malocclusion, and overgrowth of the maxillary premolar and molar teeth with subsequent ulceration of the oral portion of the mass (arrow). The mass ruptured ventrally through the skin, with extensive ulceration (arrowheads).

most common odontogenic neoplasm of the equine jaw.[7,14,19] Although ameloblastomas can be locally invasive, ameloblastomas lack features of malignancy seen in our case, including cellular atypia, widespread basaloid and spindloid cellular morphology, high N:C ratio, nuclear hyperchromatism, absence of epithelial stratification, and a high mitotic count.[5] Squamous cell carcinoma, the most common oral



Figures 5–7. Features of odontogenic histogenesis in an equine ameloblastic carcinoma. **Figure 5.** Neoplastic epithelial cells form plexiform ribbon arrangements (primitive dental lamina–like architecture). **Figure 6.** Neoplastic cells are supported by loose collagenous stroma with multifocal deposition of globular periepithelial hyalinized eosinophilic stroma (arrow).

(continued)

Figures 5–7. (continued)

Figure 7. Uncommonly, neoplastic basal cells palisade around stroma and vessels, with rare antibasilar nuclei (reverse polarity) and basal cytoplasmic clearing or vacuolation (arrowheads). Organized differentiation is absent from the peripheral basal layer into the central stellate reticulum.

neoplasm of horses,[16,19] was also considered, and various reports document this neoplasm arising from various locations in and adjacent to the oral cavity of horses.[1,6,12,15,16,20,24,25] Oral squamous cell carcinomas in the equine jaw can be poorly differentiated to the point of resembling a spindloid mesenchymal neoplasm[1,19]; careful histologic evaluation of the neoplasm is critical to establish the correct diagnosis. In our case, the presence of periepithelial hyalinized eosinophilic stroma, suggesting incomplete induction of odontoblasts,[23,26] is not considered to be a feature of squamous cell carcinoma. Furthermore, basilar palisading, basilar cytoplasmic clearing or vacuolation, and reverse nuclear polarity of the basal cells are also consistent with an odontogenic histogenesis. Last, primitive dental lamina–like architecture is supportive of a diagnosis of ameloblastic carcinoma. Dental lamina is the precursor tissue to the enamel organ, and more primitive ameloblastic tumors, which are derived from dental lamina, may recapitulate this tissue organization. However, squamous cell carcinoma can also exhibit a plexiform ribbon-type architecture that bears some resemblance to dental lamina, although the cells tend to be "less plump" appearing (personal opinion of one of the authors, B.G. Murphy).

In addition to the key morphologic features, partial dual cytokeratin–vimentin immunoreactivity of neoplastic cells is also supportive of ameloblastic cell origin. Detailed studies investigating cytokeratin and vimentin expression at different stages of odontogenesis demonstrate the transient co-expression of cytokeratin and vimentin intermediate filaments in the external enamel epithelium, internal enamel epithelium (pre-ameloblasts), and stellate reticulum cells of the enamel organ.[9,13] Furthermore, studies have demonstrated this dual expression in ameloblastoma and ameloblastic carcinoma in humans, dogs, and horses,[3,4,8–10,14,22] which likely reflects a recapitulation of the expression pattern of primitive odontogenic tissue (i.e., dental lamina or enamel organ).

To our knowledge, ameloblastic carcinoma has been reported previously in only 4 horses in the peer-reviewed literature,[3,4,14,22] with detailed, pathology-focused histologic description and images provided in only 1 case[3] (Table 1). The neoplasm involved the maxilla in 2 cases and the mandible in the other 2 cases. In both cases of maxillary ameloblastic carcinoma (case 1: 30-y-old Quarter Horse mare; case 2: 14-y-old Welsh Cob mare), disease was progressive in spite of radiation and/or chemotherapy, eventually resulting in euthanasia.[3,14] A full postmortem examination was not performed in these 2 cases, hence, evaluation for metastatic disease was not performed. In both cases of mandibular ameloblastic carcinoma, neoplasms were removed via osteotomy/partial mandibulectomy, and both patients were disease-free for at least one year post-operatively.[4,14,22] In one of the mandible cases (case 3: 9-y-old Welsh Section D gelding), the horse had additional post-operative radiation therapy, and was determined to be disease-free 17 mo post radiation.[14,22] In the other mandible case (case 4: 4-y-old Connemara mare), the horse was disease-free 12 mo after removal of the mandibular neoplasm as well as mandibular lymph nodes with confirmed metastatic disease.[14,22]

Meaningful evaluation of trends among these 5 reported cases is precluded given the low number of cases (Table 1). However, it should be noted that this neoplasm has been reported across a wide age range (4–30-y-old) and in 5 different horse breeds. Mares are overrepresented (4 of 5 cases). In the 4 cases in which histologic features were described, dual cytokeratin–vimentin immunoreactivity and a high mitotic count (7–33 mitotic figures/2.37 mm^2) were all reported consistently.[3,4,22] In 3 of these cases, basal palisading was reported.[3,22] Additionally, stellate reticulum-like cells were reported in 3 of these cases; however, in our opinion, demonstration of convincing stellate reticulum-like cells is equivocal in the published figures.[3] In all 5 cases, neoplasms exhibited marked regionally invasive and destructive behavior, but metastatic disease (confirmed in only 1 of 5 cases) was uncommon. Although these data are limited, surgical excision with or without additional adjunct therapy could be considered as therapeutic intervention for this neoplasm in horses.

Other than horses, ameloblastic carcinoma has been reported in humans,[21] a rat,[17] and 3 dogs,[8,10,11] with some variation in clinical features, histologic findings, and immunohistochemical features among species. In the case reported in a rat, the tumor arose from the left side of the mandible and exhibited locally destructive behavior, with microscopic metastatic disease identified in the ipsilateral submandibular lymph node.[17] The animal was euthanized given the poor prognosis. Histologically, all of the cardinal features of odontogenic epithelium were present, and in addition there were foci of anaplasia and squamous differentiation.[17] Neoplastic cells were immunoreactive against cytokeratin but immunonegative against vimentin.[17] All 3 of the reported canine tumors had locally aggressive behavior without evidence of metastasis, with 2 tumors arising from the mandible[8,10] and 1 tumor arising from the maxilla.[11] In all 3 cases, the neoplasms were removed surgically with no additional reported treatment, but post-operative prognosis was not reported uniformly; death occurred 2 mo post-operatively in 1 case for unknown reasons,[8] and in another case the dog was doing well 2 y post-operatively.[11] Histologic features were highly variable in these 3 cases: 1 of the cases was comprised of de-differentiated spindloid cells,[8] 1 of the canine tumors demonstrated well-differentiated neoplastic cells

Table 1. Features of reported equine ameloblastic carcinomas. Cases were identified by searching for "horse ameloblastic carcinoma" and "equine ameloblastic carcinoma" on PubMed and North Carolina State University Library databases.

Signalment	Tumor location	Metastatic disease	Histologic features	Therapy	Outcome	Reference
30-y-old F Quarter Horse	Maxilla (L)	Not evaluated	Basal palisading with anti-nuclear polarity, stellate reticulum, dual CK/Vim immunoreactivity, dental lamina architecture, periodontal ligament stroma, bone invasion, high mitotic count	Chemotherapy (intra-tumor cisplatin)	Euthanasia 4 mo after presentation	[3]
14-y-old F Welsh Cob	Maxilla (R)	Not evaluated	Not described	Radiation therapy	Euthanasia 16 mo after presentation	[14]
9-y-old CM Welsh Section D	Mandible (L)	None detected	Basal palisading, eosinophilic matrix, stellate reticulum, dual CK/Vim immunoreactivity, bone invasion, high mitotic count	Partial mandibulectomy and radiation therapy	Disease free 19.5 mo post-operative (17 mo post radiation)	[14,22]
4-y-old F Connemara	Mandible (R)	Yes, mandibular lymph node	Stellate reticulum, dual CK/Vim immunoreactivity, high mitotic count	Partial mandibulectomy	Disease free 12 mo post-operative	[4]
16-y-old F Arabian crossbred	Mandible (L)	None detected	Basal palisading, eosinophilic hyalinized matrix, dual CK/Vim immunoreactivity, dental lamina architecture, bone invasion, high mitotic count	Palliative care (oral piroxicam, wound management)	Euthanasia 4 mo after presentation	Our case

CK = cytokeratin; CM = castrated male; F = female; L = left; R = right; Vim = vimentin.

with features of ameloblastic differentiation,[11] and the last canine lesion was presumed to arise from malignant transformation of an amyloid-producing ameloblastoma.[10] Notably, vimentin immunoreactivity was only exhibited by poorly differentiated and/or spindloid neoplastic cells in 2 of these neoplasms[8,10]; otherwise, neoplastic cells were immunonegative for vimentin.

Ameloblastic carcinoma is more commonly reported in humans; however, it is still considered to be rare. In a review of 86 cases in humans,[21] the mandible was the most common location, men were overrepresented (2:1), and the neoplasm was described in a wide age range of patients (15–91 y). Interestingly, in this same case set, the 5-y survival rate was <40%, and of 68 cases in which specific treatment (surgery, radiation, and/or chemotherapy) was defined, 33 had evidence of recurrence and/or metastasis (48%). Although this pattern of biologic behavior (i.e., high rate of metastatic disease) has not been documented in veterinary species, the paucity of reported cases precludes meaningful comparisons.

A variety of other odontogenic neoplasms have been described in horses, including ameloblastoma, compound odontoma, complex odontoma, sclerosing odontogenic carcinoma, ameloblastic odontoma, ameloblastic fibroma, and odontoameloblastoma.[2,7,14,18] Notably, there is some confusion and overlap in terminology of these neoplasms in the literature (e.g., ameloblastic odontoma vs. odontoameloblastoma), which further confounds review of previous reports. Although all of these odontogenic neoplasms are considered to be rare, ameloblastoma is the equine odontogenic lesion that is reported most commonly. In our case, numerous features of malignancy differentiate ameloblastic carcinoma from ameloblastoma.

As demonstrated in our case, definitive diagnosis of oral tumors from small biopsy specimens can be a challenge. For clinical workup of a suspected odontogenic neoplasm in horses, we recommend correlation of diagnostic imaging, gross appearance, and histologic appearance of large biopsy specimens with immunohistochemical staining.

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Supplemental material

Supplemental material for this article is available online.

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