Malignant Odontogenic Oral Tumor

A case report:

Presumed ameloblastoma carcinoma in the dog

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A 6 ½ year old 47.9-kg (105.4-lb) neutered male Great Pyrenees dog presented to the Mississippi State University Animal Health Center (MSU-AHC) on March 29, 2016, for evaluation of a left mandibular mass. The mass was first noticed by owners at the end of January 2016. An incisional biopsy, dental radiographs, and bloodwork was performed in February 2016 at another referral center. The histopathology report revealed an acanthomatous ameloblastoma. After the biopsy, the dog was maintained on pain medications including Meloxicam and Tramadol. The mass continued to rapidly grow, expanding laterally and cranially. Despite the mass, the owners reported that the dog still maintained a good appetite.

On examination at MSU-AHC, a left mandibular mass was visible during panting. Hypersalivation was noted, with saliva staining on all feet. A full oral examination was done under sedation revealing a large mass originating from and displacing the second and third premolars. The mass expanded rostrally to the first premolar, caudally to the third molar, and crossed midline slightly at the lingual frenulum. A CBC, serum biochemistry analysis, and urinalysis were performed. Thoracic radiographs and computed tomography of the head with intravenous contrast (Optiray 320) were obtained.

Clinicopathologic abnormalities included a mild anemia (33%, reference range 34-60%), hyperglycemia (248 mg/dL, reference range 75-125), hyperphosphatemia (6.7 mg/dL, reference range 2.5-5.0), and mildly decreased ALT (9 U/L, reference rage 10-90). The urinalysis was within normal limits.

Radiographic findings of the thorax included airway wall mineralization of the larger bronchi, likely an incidental aging change. There was no evidence of pulmonary metastases seen. CT findings of the head included an approximately 8.8 cm x 4.4 cm x 4.0 cm, heterogeneous, mixed density (fluid, soft tissue, and mineral), sharply marginated mass surrounding the left mandible from the level of the first premolar to the rostral aspect of the ramus. The mass demonstrated moderate to marked, heterogeneous contract enhancement, more so on the delayed images obtained approximately 2 minutes after contrast injection. There was severe moth eaten lysis of the adjacent left mandible with cortical destruction. The mass was located within the bone causing dorsal displacement of the associated teeth and rightward and dorsal displacement of the tongue. There was also amorphous periosteal new bone associated with the mass. The left mandibular lymph node and left medial retropharyngeal lymph node were slightly larger than the right.

On the basis of these results, a left hemimandibulectomy procedure was recommended to the owner with the understanding that due to the extensive nature of the mass, complete surgical removal of the tumor may not be feasible. The owner elected to pursue surgery, which was performed the following day on March 30, 2016.

Under general anesthesia, the patient was placed in right lateral recumbency, oblique partially toward sternal recumbency. The ventral mandible and left neck were clipped and prepped aseptically using 4% chlorhexidine scrub and the mouth was also prepped with a chlorhexidine solution and then draped in a sterile fashion. A skin incision was made with a No. 10 blade extending caudally from the left lip commissure. A 1 cm soft tissue margin was measured in all

directions from the intraoral portion of the mass and the gingiva and oral mucosa was incised along this margin. Where not involved with the mass, the gingiva was incised along both the mesial and buccal alveolar borders. Hemostasis was maintained with monopolar cautery as needed. The mucosal incision crossed to the right of midline at the level of the lingual frenulum and the sublingial salivary caruncles. Both sublingual salivary ducts were incised, but were not ligated. The mandibular symphysis was split with an 8mm osteotome and mallet. The muscles of mastication and gingiva were elevated from the bone and transected. The mandibular alveolar artery was ligated using a large hemoclip and transected. The temporomandibular joint was located by manipulating the mandible and palpating the articulation. The joint capsule was incised with a No. 15 blade and disarticulated allowing removal of the left hemimandible. The surgical site was lavaged with sterile saline. The masticatory muscles were apposed ventrally with 3-0 polydioxanone in a horizontal mattress pattern. The buccal mucosa was apposed to the lingual mucosa with 3-0 polydioxanone with a combination of simple interrupted and simple continuous patterns. A cheiloplasty was performed and the oral mucosa was closed with 3-0 polydioxianone in a simple interrupted pattern, followed by subcutaneous tissue with 3-0 polydioxanone in a simple continuous pattern. Skin was apposed with 3-0 nylon in a cruciate pattern. The surgery and recovery from anesthesia was uneventful. The entire left mandible was submitted to Mississippi State University Pathology Service for histopathology.

The dog was maintained on IV fluids with lactated Ringer's solution (2 mL/kg/hr) and a constant rate infusion of morphine (0.1 mg/kg/hr) immediately after surgery for the first 24 hours. Dexmedetomidine (0.2 mcg/kg, PRN q6h) was used as needed for anxiety. He was NPO for the first 24 hours and the morphine infusion was incrementally decreased and discontinued 24 hours after surgery. Beginning at that time, Tylenol 4 suspension (30mg/mL at 2 mg/kg of codeine, q8h) and amoxicillin (800 mg, q12h) was administered by mouth.

The dog was sedated one day following surgery to repair a minor dehiscence near the left commissure of the lip. A small amount of debridement was performed, followed by closure with 3-0 polydioxanone in a simple interrupted pattern. Two days following surgery, the dog was discharged to the owner. At that time, the dog was comfortable, drinking water, and eating wet food meatballs by hand. The owners were instructed to administer Tylenol 4 suspension (2 mg/kg q8h), amoxicillin (800 mg, q12h), Meloxicam (continue as directed from regular veterinarian), and to return the dog for reevaluation in 10-14 days.

Three days after discharge on April 4, 2016, the dog was reevaluated at the veterinary medical teaching hospital because incision had dehisced. The owners were unable to give oral medications; however, the dog was still eating and drinking at home. The dog's lower lip was drooping and was no longer opposed to the mucosal tissue of the left lip. A full oral examination was performed under sedation revealing the entire incision was dehisced, with mucosal necrosis. During the same sedation episode, a dehiscence repair procedure was performed, with closure relatively identical to that previously described. Additionally, two buttons were placed as stents on the lateral aspect of the left lip commissure to relieve tension. The dog was readmitted to the hospital where an IV catheter was placed for easier access for sedation. Oral antibiotics were discontinued due to unwillingness to eat and he was given a subcutaneous, long lasting injectable

antibiotic, Cerenia (8 mg/kg). Meloxicam (0.1 mg/kg q24h) was given subcutaneously for pain control and a compounded mouth rinse was initiated (lidocaine 2% 150 mL, Benadryl 12.5 mg/mL 20 mL, and Oxytetracycline 1.7 g, q4-6h, PO). Due to his temperament, the mouth rinse was discontinued 48 hours after starting. Acepromazine (0.01 mg/kg, PRN q4h) and Hyrdomorphone (0.1 mg/kg, PRN q4h) were both used for rescue subcutaneously if needed for pain. His appetite improved slightly during this stay, but he continued to be fasted and sedated every other day for reevaluation of the incision and minor dehiscence repairs. On sedated reevaluation on April 6, 2016, bone anchoring sutures were placed in the rostral aspect of the incision due to dehiscence of the most rostral aspect and dead mucosal tissue was debrided from the caudal aspect of the incision. Tramadol (2 mg/kg, q8h PO) was added to help minimize the pain after dehiscence repairs. Two areas of the caudal incision dehisced and were replaced with a double row in a continuous pattern on April 8, 2016 and the lateral buttons were removed.

During the sedated oral examination on April 10, one minor area of dehiscence was repaired and a recheck CBC and serum biochemistry analysis was performed. Clinicopathologic abnormalities included a stress leukogram, mild hypoalbuminemia (2.2 g/dL, reference range 2.5-3.9), and mildly elevated creatinine (1.83 mg/dL, reference range 0.50-1.40). Meloxicam was discontinued since his pain was adequately controlled by Tramadol and his hypoalbuminemia was thought to be due to his decreased appetite. Granulation tissue was noted at the lip commissure during his sedated oral examination on April 14 and no new sutures were placed.

The pathology report had been finalized during his hospitalization. Gross evaluation of the left mandible by the pathology revealed a fracture in the mid body of the mandible. On cut surface, granular and moderately firm white tissue was evidence with very minimal residual remnant of bone at the level of the mid tumor. The mass was easily cut with a knife completely across the mandible and tumor. The tumor tissue extended to the loose alveolar connective tissue that was inked blue on the periphery. The tumor also extended within the medullary cavity of the caudal body of the mandible beyond the obvious extent of the major mass. Multiple large sections examined were taken in transverse planes through the mandibular tumor. Histologically the mass consisted of variable sized lobules that were isolated by generally broad bands of cellular fibrous connective tissue. Occasional woven bone trabeculae occurred within the fibrous septa. The lobules were round to irregular and consisted of sheets of relatively bland homogenous well individualized epithelial cells with high nuclear to cytoplasmic ratio. There was no evidence of peripheral palisades along the periphery of the well demarcated lobules at the interface with the connective tissue septa. Frequently, variable sized cystic or pseudo cystic spaces within the sheets of cells contained pale basophilic vacuolated fluid. Individual cells had round to ovoid pleomorphic nuclei that were open faced with inconspicuous chromatin and small nucleoli. The cytoplasm was scant, basophilic, and sometimes vacuolated. The mitotic index was fairly high; 9 mitotic figures were counted in 10 high power fields. Superficially and sometimes along the periphery, neoplastic cells occurred in endothelial lined blood filled spaces as tumor emboli. Immunohistochemical findings revealed strong positive Vimentin staining of the cellular mesenchymal stroma surround islands of odontogenic epithelium. Within the epithelial islands, randomly interspersed stellate cells approximately stained 10-20%. A cytokeratin stain revealed that the epithelial like islands only stained sporadically in about 10% of the cells for cytokeratin.

Based on the characteristics of the tumor cells, this tumor was classified as a poorly differentiated and malignant odontogenic tumor, which are very rare in dogs.

Prior to discharge on April 16, the patient was sedated one last time to recheck the incision. All sutures appeared to be intact; however, an approximately 3-4 mm ulceration on the hard palate, just caudal to the incisors was noted, likely due to ulceration from right lower canine impingment due to mandibular drift. The dog was discharged to the owners for the second time 17 days post-surgery. At that time, the dog was comfortable, drinking water, and eating multiple, small amounts of wet food meatballs by hand. The owners were instructed to administer Tramadol (2 mg/kg, q8h PO) and to return in one week for a recheck and vital pulpotomy of the right lower canine.

The dog presented back to Mississippi State University Animal Health Center on April 21, 2016 for a recheck examination and vital pulpotomy of his right lower canine tooth under general anesthesia. The surgical incision started to epithelize and heal. Sutures on the lateral aspect of the lip were removed; however, the sutures rostrally were left to eventually dissolve. A dental prophylactic cleaning and vital pulpotomy were performed to prevent further rubbing of the right lower canine and hard palate. The dog was discharged to the owners the same day. The owners were instructed to administer Tramadol (2 mg/kg, PO q8h) and to set up an appointment with Internal Medicine Service for an oncology consultation at their earliest convenience if interested in pursuing treatment options. A recheck oral examination in 2-3 months, chest radiographs, and lymph node evaluation was recommended.

The owners presented back to Mississippi State University Animal Health Center on May 5, 2016 for an oncology consultation. The owners were told that the best option for malignant odontogenic tumors is surgical removal with wide margins. Although the dog underwent a left hemimandibulectomy, wide surgical margins were unable to be achieved due to the extensive nature of the tumor and its location. The gold standard for this type of tumor treatment is stereotactic radiation therapy; however, the owners declined due to the cost of traveling. The owners elected to pursue chemotherapy for a course of 3-6 months with close monitoring of the surgical site and lymph nodes for any tumor regrowth or metastasis. Recheck thoracic radiographs were recommended every 3 months. Physical exam at this time was unremarkable, all lymph nodes were small, and the oral incision was healed. A CBC and serum biochemistry analysis was performed prior to starting chemotherapy. The dog was started on a metronomic protocol of Cyclophosphamide (2 mg/m^2, q24h PO for 3 days) and Piroxicam (0.3 mg/kg PO q24h). Metronidazole (7.5 mg/kg, PO PRN), Ondansetron (0.3 mg/kg, PO PRN), and omeprazole (1 mg/kg, PO PRN) were also prescribed as needed for any adverse side effects of the chemotherapy. The owners were instructed to administer the metronomic protocol at home and return in two weeks for a recheck of bloodwork and urinalysis.

At the recheck examination on May 19, 2016, physical examination was unchanged from the previous visit. The owners reported that the dog was doing well at home and completely adjusted to eating and drinking. A CBC, serum biochemistry analysis, and urinalysis was performed. The only clinicopathologic abnormality was a mild thrombocytopenia on manual count (128 K/uL, reference range 160-650). The chemotherapy protocol was continued and the owners were

instructed to return in another two weeks for a recheck of bloodwork and urinalysis before decreasing recheck visits to monthly.

The next recheck examination on June 2, 2016, was unchanged from previous. A CBC, serum biochemistry analysis, and urinalysis was performed; all within normal limits. The chemotherapy protocol was continued and the owners were instructed to return in one month for another recheck. His monthly recheck on June 30, 2016, again was unchanged and the owners reported that he was doing very well at home and very active. The chemotherapy protocol was continued and the owners were instructed to return in six weeks for a full recheck including thoracic radiographs.

The dog returned August 18, 2016, for a full recheck including thoracic radiographs. The owners reported that he continued to be doing well at home; however, he did have one episode of vomiting two weeks prior that resolved. Physical exam was unremarkable and lymph nodes were within normal limits. A CBC, serum biochemistry analysis, and urinalysis was performed; all within normal limits. Thoracic radiographs revealed a miliary, structured interstitial pattern with consideration given to neoplastic or fungal etiology. Multiple fine needle aspirates of the lungs were submitted for cytology; however, they were non-diagnostic. A urine antigen test was submitted to test for fungal antigens. In the meantime, Cyclophosphamide was discontinued. The owners were instructed to continue to administer Piroxicam (0.3 mg/kg, PO q24h), Omeprazole (1 mg/kg, PO q24h), and start Doxycycline (6 mg/kg, PO q24h). The recommended next step to be a bronchoalveolar lavage or lung biopsy via thoracoscopy to determine the origin of the lung pathology.

The urine antigen fungal test was negative and therefore the likely cause of the lung pathology was thought to be metastatic disease; however, a definite diagnosis would require further diagnostics. The owners elected to recheck thoracic radiographs after a two week course of Doxycycline and forgo further diagnostics. The dog presented on September 1, 2016, for recheck thoracic radiographs which revealed mildly worsening diffuse, military, structured interstitial pulmonary pattern. The owners were instructed to monitor the dog’s quality of life and continue on Piroxicam (0.3 mg/kg, PO q24h) and Omeprazole (1 mg/kg, PO q24h).

On January 3, 2017, the dog presented to Mississippi State University Animal Health Center for regrowth of the oral mass. The owners first noticed the regrowth within the past week; however, the dog continued to eat and drink normally at home. The owners also reported that the dog was not showing any signs of respiratory distress. Physical exam revealed regrowth of the mass along the right mandible with an indentation and ulceration of the mass from the upper right canine. A CBC and serum biochemistry analysis was performed and was within normal limits. Thoracic radiographs revealed moderate to marked progression of the previously described miliary interstitial pattern. There were numerous nodules present ranging in size from 1 mm to 2 cm. An ill-defined, soft tissue opacity of 2.4 cm is present just dorsal to the second sternebra, thought to be sternal lymphadenopathy with progressive, metastatic disease. Palliative care was discussed with the owners and they elected to try Palladia (2.6 mg/kg, PO every other day). The owners were instructed to follow up with their regular veterinarian to check urine protein: creatinine

ratio, blood pressures, and serum biochemistry analysis at 2 weeks, 4 weeks, and then every 4-6 weeks after initiation of the chemotherapy protocol.

The dog has not presented to Mississippi State University Animal Health Center since January 2017; however, the owners are continuing him on the Palladia protocol. The owners do report that he continues to do well at home and has not had any respiratory signs as of April 2017.

Discussion:

Odontogenic tumors are an umbrella term used to describe oral tumors originating from tissues that are components of the tooth forming apparatus or their embryonic remnants.[1,3] Historically in veterinary medicine, epulides were described as tumors arising from the periodontal ligament and were classified as fibromatous, ossifying and acanthomatous. By the classical definition and as it is utilized in human medical nomenclature, epulis is a more general term used to describe any gingival swelling.

Epulides can be divided into three categories: reactive lesions, odontogenic tumors and cysts, and non-odontogenic tumors.[1] In all cases, incisional biopsy is important because treatment and prognosis vary greatly between this diverse group of lesions. Reactive lesions include gingival hyperplasia and focal fibrous hyperplasia, which are benign and can be treated medically or with marginal surgical excision in most cases. Non-odontogenic tumors are typically malignant and include melanoma, squamous cell carcinoma and fibrosarcoma, and are treated with wide surgical margins and typically adjunctive therapy. Odontogenic tumors are further classified according to their tissue of origin – epithelial, mesenchymal, or mixed.[1] Mesenchymal tumors include peripheral odontogenic tumors (formerly ossifying and fibromatous epulides). These can be treated with marginal excision or with excision and conservative bone removal. Epithelial tumors in include ameloblastoma, which have been further divided into central or canine acanthomatous ameloblastoma, which are both locally aggressive and treated with wide surgical excision, but do not metastasize.

Malignant odontogenic tumors are rare in human medicine and they are even more rarely reported in veterinary medicine. A classification system was set forth by Slootweg and Muller, categorizing tumors of ameloblastic differentiation and present cytologic features of malignancy regardless of whether there is metastasis or not.[4,6] There are two forms in human literature that are described including malignant ameloblastoma and ameloblastic carcinoma. According to the classification system, a malignant ameloblastoma is a tumor that has a benign cytologic appearance, but metastasized with well differentiated lesions and does not have any cellular features of malignancy. An ameloblastic carcinoma on the other hand, has combined cellular features of an ameloblastoma and carcinoma, regardless of metastatis.[4,6] In humans, ameloblastic carcinoma is very aggressive; although metastasis is rare, it usually occurs in the lungs, followed by cervical lymph nodes, spine, and bone.[4]

To this date, there have only been a few case reports in veterinary medicine describing ameloblastic carcinoma, one in a horse and the others in dogs, one of which had prominent formation of bone and cytological signs of malignancy.[2,4] One of the previous case reports describes an ameloblastic carcinoma in a 3 year old Alaskan Malamute. Histologic examination of the tumor had evidence of an ameloblastoma, ameloblastic epithelium spread in a fibrous

stroma; however, there was also cellular pleomorphism, high mitotic rate, and a high cytoplasm to nucleus ratio, much like the case we described.[4] The previously described case had positive immunohistochemical labeling to cytokeratin. Studies in human odontogenic tumors have found co-expression between cytokeratins and vimentin in certain neoplasms, eliciting the development of the tumor from both the epithelium and mesenchymal tissues.[4]

The Alaskan Malamute in the previously described case study underwent a partial hemimaxillectomy. There were no signs of metastasis seen on thoracic radiographs and local lymph nodes were normal in size. No follow up radiation or chemotherapy were pursued. The dog continued to be doing clinically well two years following surgery; however, no more follow up was available since the time of the published study. In the case study involving the 30 year old Quarter Horse, a mass as noted on the hard palate, displacing ventrally surrounding the second premolar.[2] A conservative, palliative therapy of intralesional cisplatin was initiated; however, it was discontinued after two treatments due to lack of clinical response and the mare was euthanized four months after initial presentation.[2]

Another recently published study looked at five dogs with a variant of acanthomatous ameloblastoma. Histologically, all of these tumors had atypical, pleomorphic cells with a high mitotic rate; nevertheless, they were all immunohistochemically negative for vimentin and cytokeratin. Complete surgical removal was achieved in three of the dogs via maxillectomy or mandibulectomy; however, the remaining two dogs had incomplete margins. Ancillary therapy was not initiated in any patient and no local recurrence or distant metastasis was reported in any case at follow up of 6-30 months.

Finally, a single case report of an 11 year old, male Collie described an oral tumor in which surgeons attempted to surgically excise. The tumor recurred within a month of removal and the dog died of multiple organ failure two months after the original surgical excision. Postmortem examination revealed the extensive local invasion of the tumor into the nasal cavity, maxilla, and base of the skull with similar masses in other organs including the mandibular lymph nodes, liver, lung, and orbital cavity[8]. Histological examination of the masses in the lungs revealed material resembling dysplastic dentine or enamel matrix[8]. This study was the first known report of possible malignant ameloblastic fibro-odontoma in a dog with metastasis to distant organs[8].

The treatment of choice for malignant odontogenic tumors in dogs is wide surgical excision via partial maxillectomy or mandibulectomy. Adjunctive therapy including chemotherapy and radiation may be indicated, but there is little published data to guide treatment due to the rare nature of this condition in dogs.

In humans, the standard of care for malignant odontogenic tumors is wide surgical margins of 1 centimeter followed by radiation; however, tumor recurrence is common.[7] Following wide local excision of acanthomatous ameloblastomas, one author reported a one year survival rate of 100% among 25 dogs, while another study reported a 97% one year survival rate among 42 dogs due to local recurrence of the tumor.[1]

In this case, the initial diagnosis of acanthomatous ameloblastoma was made via incisional biopsy. Treatment with wide excision including 1 cm margins was attempted. This was complicated by the large size of the mass and its encroachment toward midline. Post-operative morbidity including repeated episodes of dehiscence that may have been related to excessive tension, especially from the sublingual reconstruction or possibly transection of the sublingual

salivary ducts. It has been reported that ligating sublingual salivary ducts is not necessary following transection with mandibulectomy, but the authors suspect that may have been involved in the repeated dehiscences of the surgical incision.

More aggressive local excision to achieve local control would have been challenging in this case, considering the extent of the mass. Radiation therapy was considered as an adjunct to achieve local control, but was declined in this case by the clients. Little information is available regarding chemotherapy regimens for malignant odontogenic tumors, and a metronomic protocol was selected. It is possible that a different chemotherapeutic protocol could have achieved more successful results in this case.

In conclusion, the authors present a case of a malignant odontogenic tumor treated with hemimandibulectomy resulting in successful local control of the tumor for approximately 7 months. Probable lung metastases to were noted 3 months following surgery. Malignant odontogenic tumor, while rare, should be considered as a differential diagnosis for oral tumors in dogs. Aggressive treatment with multimodal therapy may be indicated, but long-term prognosis may be poor based on the results of this case.

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