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Case Report

Oral Squamous Cell Carcinoma in a Pigtailed Macaque (*Macaca nemestrina*)

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An adult, gravid, female pigtailed macaque (*Macaca nemestrina*) presented for facial swelling centered on the left mandible that was approximately 5 cm wide. Differential diagnoses included infectious, inflammatory, and neoplastic origins. Definitive antemortem diagnosis was not possible, and the macaque's condition worsened despite supportive care. Necropsy findings included a mandibular mass that was locally invasive and expansile, encompassing approximately 80% of the left mandibular bone. The mass replaced portions of the soft palate, hard palate, sinuses, ear canal, and the caudal–rostral calvarium and masseter muscle. Histologically, the mass was a neoplasm that was poorly circumscribed, unencapsulated, and infiltrative invading regional bone and soft tissue. The mass consisted of polygonal squamous epithelial cells with intercellular bridging that breached the epithelial basement membrane and formed invasive nests, cords, and trabeculae. The mitotic rate averaged 3 per 400× field of view, with occasional bizarre mitotic figures. Epithelial cells often exhibited dyskeratosis, and the nests often contained compact lamellated keratin (keratin pearls). The neoplasm was positive via immunohistochemistry for pancytokeratin, variably positive for S100, and negative for vimentin, smooth muscle actin, and desmin. The gross, histologic, and immunohistochemical findings were consistent with an aggressive oral squamous cell carcinoma. The neoplasm was negative via PCR for papilloma virus. In general, neoplasia in macaques is rare. Although squamous cell carcinomas are one of the most common oral neoplasia in many species, to our knowledge this case represents the first reported oral squamous cell carcinoma in a pigtailed macaque.

Abbreviation: SCC, squamous cell carcinoma.

Squamous cell carcinomas (SCC) are one of the most commonly reported oral tumors. They are characterized as firm, nodular to irregular, soft-tissue masses that are often ulcerated.[6] These tumors are frequently highly invasive to local bone and muscle and occasionally metastasize to local and regional lymph nodes.[6] Histologically, SCC are characterized by keratin pearls, intercellular bridges, and positive cytokeratin staining on immunohistochemistry.[6,18] SCC have been associated with carcinogen exposure (such as bracken fern toxicosis in cattle), actinic radiation, and rarely with papillomatosis.[8]

In general, neoplastic diseases are rare in nonhuman primates, and SCC and lymphoma are the 2 most commonly reported oral neoplasms in these species.[3] SCC have most commonly been reported in rhesus macaques (*Macaca mullata*) and baboons (*Papio* spp.) among nonhuman primate species.[9] In rhesus macaques, SCC has occurred in the oral cavity,[9] integument,[9,22] esophagus,[9] stomach,[21] lung,[9,13] prepuce–penis,[10] cervix,[9] uterus,[9] and eye.[9] These neoplasms have also been reported to occur in cynomolgus macaques,[14,15,17,19] marmosets, squirrel monkeys, tree shrews, capuchins, tamarins, black spider monkeys, sooty mangabies, a spectacled langur, and an orangutan.[9] No report describing SCC in a pig-tailed macaque has been published previously. The oral cavity is the most common site of SCC in nonhuman primates, and metastasis occurs in approximately 23% of cases.[9] The average age at diagnosis of oral SCC in rhesus macaques is 17.6 y.[22] In baboons, SCC is the third most common neoplasm, after intestinal adenocarcinoma and lymphosarcoma.[4] The following case report describes an oral SCC in a pregnant pig-tailed macaque.

Case Report

In August 2009, a 9-y-old breeding female pig-tailed macaque (*Macaca nemestrina*) presented at the Washington National Primate Research Center to the veterinary staff for facial swelling. The animal originated at the center's breeding colony at Tulane facility (Tulane National Primate Research Center, Covington, LA), and for the past 3 y had been located in Seattle as part of the center's timed breeding colony. She had 4 previous pregnancies and was gravid at the time of presentation. The first 3 pregnancies resulted in viable births that were delivered naturally; the fourth pregnancy was delivered via cesarean section for experimental purposes. She was negative for simian retrovirus 2 according to ELISA and PCR assay, negative for simian T-lymphotrophic virus according to ELISA, and positive for *Macacine herpesvirus 1* antibodies according to ELISA. The macaque was housed in

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accordance with the regulations of the Animal Welfare Act and the recommendations of the *Guide for the Care and Use of Laboratory Animals*.[1,11] All procedures performed were approved by the IACUC of the University of Washington.

On cageside exam, the macaque was bright, alert, and responsive, with normal stools and urine. A swelling was noted on the left jaw, and a small amount of blood was present on the outer surface of the cheek over the swelling. The macaque was sedated (10 mg/kg ketamine and 0.04 mg/kg atropine); physical exam revealed a large swelling of the left mandible; the mass occupied the majority of the left cheek pouch. The width of the mass at the left mandibular ramous was wide enough to extend past the rostral mandibular symphysis (midline) and appeared to include the rostral portion of the right mandible. The mucosal membrane lining of the left cheek had an area of ulceration over the mass. There was an ovoid abrasion on the skin surface of the cheek which extended from the left commissure of the lip to approximately 8 cm laterally. A fine-needle aspirate from the center of the mass was obtained, and approximately 6 mL blood was collected. The cytology of the aspirated material was consistent with whole blood, and there was no growth on culture. The macaque's CBC analysis was within normal limits; serum chemistry revealed moderate hypoalbuminemia (1.6 g/dL; normal, 3.5 to 5.2 g/dL), a low albumin:globulin ratio (0.308; normal,1.0), and mild elevations in BUN (24 mg/dL; normal, 8 to 21 mg/dL), ALP (519 U/L; normal, 26 to 98 U/L), and GGT (100 U/L; normal, 0 to 55 U/L). In addition, mild hypercalcemia (10.6 mg/dL corrected; normal, 8.9 to 10.2 mg/dL) emerged after correction for the hypoalbuminemia. Treatment with amoxicillin–clavulanic acid (11 mg/kg PO twice daily; Clavamox, Pfizer Animal Health, Exton, PA), ketoprofen (5 mg/kg PO twice daily; Teva Pharmaceuticals, Sellersville, PA), Milk and Egg Protein Powder (1 tablespoon PO twice daily; MLO Products, Tulsa, OK), and prenatal vitamins (1 tablet PO daily; CompleteNate, Trigen Laboratories, Sayerville, NJ) was initiated. Abdominal ultrasonography confirmed a viable 124-gestation-day fetus.

Radiographs obtained 3 d after presentation revealed a mass in the left mandible and rostral portion of the right mandible. The mass was expansile and osteolytic. Differential diagnoses for the mass included infectious, inflammatory, and neoplastic processes. Because of the poor prognosis for the macaque, the decision was made to provide supportive care until delivery of the infant. The treatment plan was extended to include calcium carbonate (50 mg/kg PO twice daily; GlaxoSmithKline, St Louis, MO). A follow-up exam performed 7 d after the initial presentation revealed no change in condition, and the fetus was stable.

At 16 d after presentation, an additional oval abrasion (width, approximately 5 cm) superior to the left ear occurred, and the macaque was not eating her oral medication. Injectable ketoprofen (5 mg/kg IM twice daily; Fort Dodge, Fort Dodge, IA) and cefazolin (25 mg/kg IM twice daily; West-Ward Pharmaceutical, Eatontown, NJ) were initiated; the macaque was offered moistened biscuits, and the food intake increased to normal. Follow-up radiographs, CBC analysis, serum chemistry, and assessment of erythrocyte sedimentation rate were performed the subsequent day. Radiographs revealed increased osteolysis of the left mandible and the rostral portion of the right mandible. CBC analysis revealed anemia (PCV, 30%; normal, 36% to 45%). The erythrocyte sedimentation rate was elevated (104 mm/h; normal, less than 20 mm/h), and the chemistry evaluation revealed hypoalbuminemia (1.4 mg/dL; normal, 3.5 to 5.2 g/dL) and a low albumin:globulin ratio (0.264; normal,1.0). The mild elevations in ALP (519 U/L; normal, 26 to 98 U/L) and GGT (100 U/L; normal, 0 to 55 U/L) persisted. One day later (18 d after presentation), the macaque was noted to have eaten poorly and showed a slight decrease in body weight (3% in 5 d). Both the dam and infant were euthanized, because the infant (141 d of gestation) was deemed to be too immature to sustain life.

Pathology

At necropsy, the mandibular mass was found to be a locally invasive, expansile tumor that encompassed approximately 80% of the left mandibular bone and that crossed the symphysis to involve the mandible supporting the right incisor tooth. Neoplastic tissue was firm (but could be sectioned with a scalpel blade) and replaced the mandibular bone. On section at the premolars, which was the widest portion of the mass, the mass was roughly spherical (3.5 cm × 4 cm), with the predominance of proliferative tissue located on the buccal side of the mandible (Figure 1). Neoplastic tissues replaced portions of the soft palate, hard palate, sinuses, ear canal, and the caudal–rostral calvarium. Intracalvarial neoplastic tissue was visible through the dura but did not significantly compress the brain. As much as 90% of the masseter muscle was replaced by neoplastic tissue. Overlying salivary glands and underlying lymph nodes were compressed but not grossly involved in the mass. Teeth, gingival, and glossal tissues were intact; mucosal ulceration was not evident.

The neoplastic tissues were poorly circumscribed, unencapsulated, and infiltrative; polygonal squamous epithelial cells with intercellular bridges breached the epithelial basement membrane and formed nests, cords, and trabeculae, which were supported by moderate amounts of fibrovascular stroma. Cells had variably distinct borders, with abundant amphophilic to eosinophilic cytoplasm, and contained a single, irregularly round nucleus with finely stippled chromatin and 1 to 4 distinct magenta nucleoli. The mitotic rate averaged 3 per 400× field of view, with occasional bizarre mitotic figures. Neoplastic cells ranged from well-differentiated and organized to dysplastic and featuring dyskeratosis, anisokaryosis, and anisocytosis; intercellular bridges were visible between well-differentiated neoplastic cells. Most nests contained central, eosinophilic accumulations of compact lamellated keratin (keratin pearls). Moderate pyogranulomatous inflammation extended from the epidermis into deep tissues. The architecture and boundaries of bone, muscle, glandular, and connective tissues often were obliterated by invasive neoplastic cells; neoplastic tissues extended from the ulcerated epidermis through the deep dermis and into connective tissue and bone. Metastases were not identified in regional lymph nodes or elsewhere. The neoplasm was positive via immunohistochemistry for pancytokeratin, variably positive for S100, and negative for vimentin, smooth muscle actin, and desmin (Table 1). Histologically, the neoplastic mass was consistent with an aggressive SCC (Figure 2).

Additional histologic findings included multifocal, mild lymphohistiocytic and fibrosing myocarditis and diffuse, mild lymphoplasmacytic and eosinophilic enterocolitis. DNA was isolated from the tumor tissue for use as template in PCR amplification by using consensus degenerate hybrid oligonucleotide primers targeting diverse members of the papillomavirus family, essentially as described previously.[23] The sample was negative for papillomavirus.

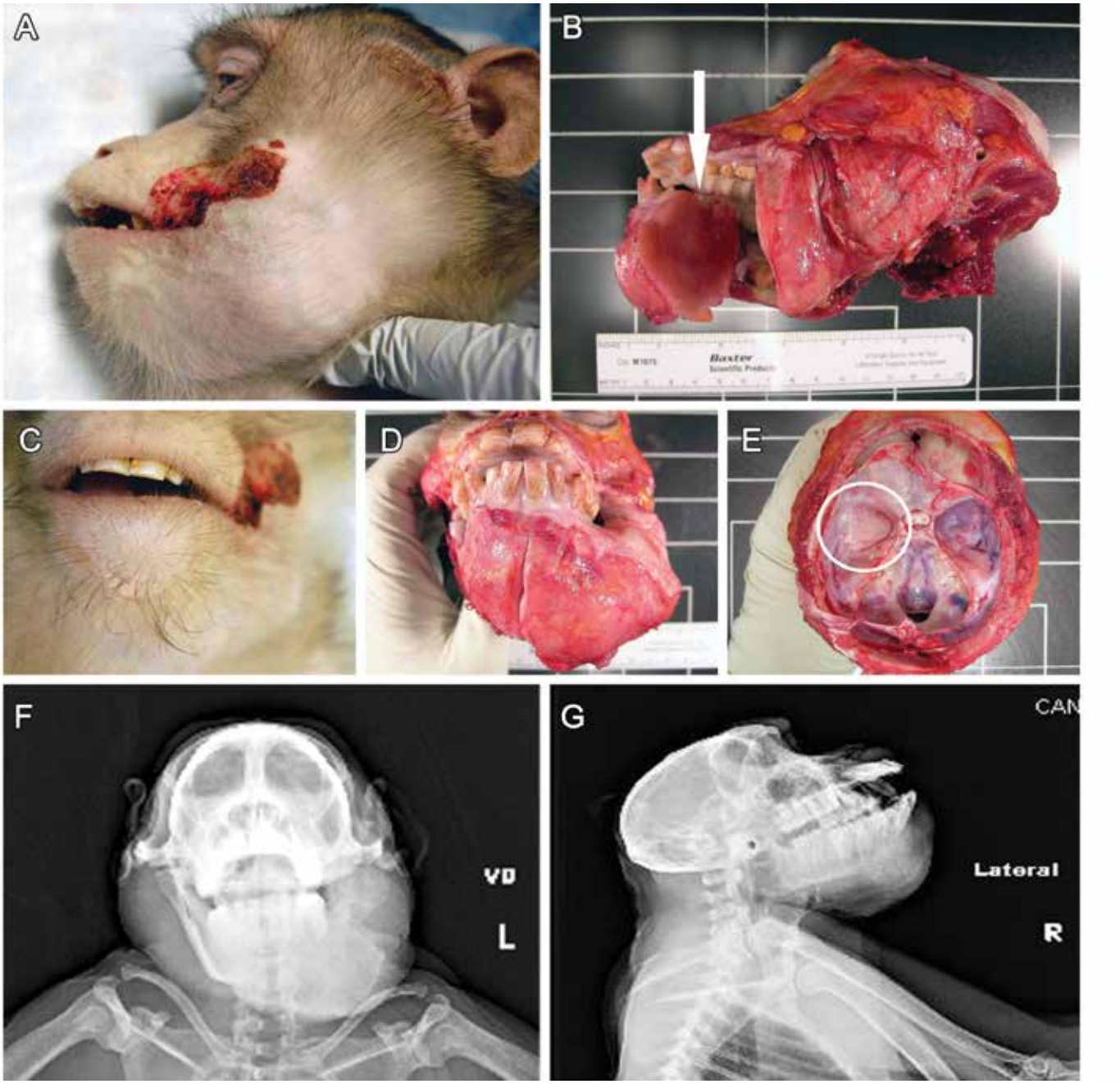

Figure 1. Gross and radiographic findings. (A) Animal at gross necropsy imaged in right lateral recumbancy. The epidermis overlying the left cheek is ulcerated from the buccal margin and along the maxilla. The left maxilla and mandible are expanded by a firm tissue mass. (B) Section of the skull at gross necropsy imaged in right lateral recumbancy. A wedge section of the mass was removed with a scalpel and demonstrates maxillary bone loss and replacement. Neoplastic tissues (3.5 × 4 cm) extend from the epithelium, through the bone, to the mucus membranes and gingiva (arrow). Horizontal white lines on the photo stand are 2.5 cm apart. (C) Rostral image of animal at gross necropsy; the epidermis overlying the left maxilla (cheek) is ulcerated and excoriated. The left maxilla and mandible are enlarged. (D) Rostral image of skull at gross necropsy; the neoplasm expands the left maxilla, crossing the midline. (E) Cross-sectional image of the skull taken at gross necropsy, brain removed. Note the different opacities and color of the calvarial tissues on either side of the optic chiasm. The tumor has invaded the bone on the left side (white to pink tissues are circled); the right side is unaffected. (F) Antemortem radiographic image of the skull, ventrodorsal view. Note the expansile, osteolytic lesion of the left mandible, with invasion across the symphysis. (G) Antemortem radiographic image of the skull with the animal in the right lateral position. Note the expansile, osteolytic lesion on the mandible.

Discussion

To our knowledge, this report describes the first case of SCC in a pigtailed macaque. SCC have been reported in other macaque species and have involved the tongue, gingiva, esophagus, gastric cardia, eye, lungs, penis, mammary areas, and cervix.[4] However, the oral cavity is the most common site in macaques.[4] Oral SCC vary in size and can be flat to proliferative. These lesion also vary from well-differentiated cells that include whorls of keratin

Table 1. Reagents, controls, and staining results for immunohistochemistry

Marker	Expected result in neoplastic tissues	Internal control	Primary antibody, dilution	Secondary antibody, dilution	Negative-control antibody, dilution
Smooth muscle actin	Negative	Arterial wall smooth muscle, intestinal tissue	SMA clone 1A4,[a] 1:1000	Biotinylated antimouse[b], 1:200	Mouse antiinsulin,[c] 1:1000
Desmin	Negative	Uterus	Desmin clone D33,[d] 1:100	Biotinylated antimouse,[b] 1:200	Mouse antiinsulin,[c] 1:1000
Pancytokeratin	Positive	Skin	Cytokeratin clone MNF116,[e] 1:100	Biotinylated antimouse,[b] 1:200	Mouse antiinsulin,[c] 1:1000
S100	Variable	Brain	Dako Z0311; 1:400	Biotinylated antirabbit,[f] 1:200	*Helicobacter pylori*,[g] 1:400
Vimentin	Negative	Skin with fibrous tissue	Vimentin clone V9,[h] 1:25	Biotinylated antimouse,[b] 1:200	Mouse antiinsulin,[c] 1:25

[a]Catalog number M0851, Dako (Carpinteria, CA)
[b]Catalog number PK6102, Vector Laboratories (Burlingame, CA)
[c]Catalog number 18-0066, Zymed Laboratories (San Francisco, CA)
[d]Catalog number M0760, Dako
[e]Catalog number M0821, Dako
[f]Catalog number PK6101, Vector Laboratories
[g]Catalog number B04071, Dako
[h]Catalog number M0725, Dako

(keratin pearls) and desmosomes (intercellular bridges) to undifferentiated cells with high mitotic activity.[18] The average age of affected nonhuman primates is 11.9 ± 1.2 y.[4] Metastasis occurs in approximately 23% of all cases in nonhuman primates[4] but was not seen in the case we report here.

The additional histology findings of multifocal, mild lymphohistiocytic and fibrosing myocarditis and enterocolitis were clinically nonrelevant in our macaque. The cardiac inflammation and fibrosis were clinically silent; the macaque ausculted within normal limits as close as 24 h prior to euthanasia. Enterocolitis is prevalent in the center's colony and likely is not associated with the neoplasia.

Immunohistochemistry can be used to assist in the diagnosis of SCC, as done in the presented case (Table 1). In humans, oral SCC are responsible for an estimated 7600 deaths annually. In addition, men are affected twice as frequently as are women.[5] Oral SCC in humans are strongly associated with tobacco and alcohol use.[5] Alterations in p16, p53, pRb, and cyclin D1 expression and upregulation of epidermal growth factor receptor have all been reported to occur in SCC of the human head and neck.[5] The S100 family of calcium-binding proteins includes 21 members, 14 of which are located within the same epidermal differentiation complex (1q21), and are involved in cell growth, phosphorylation, and cell-cycle regulation—including transcription, apoptosis, and cell survival—and regulation of cytoskeleton components. S100 has been reported to be downregulated in some SCC of the human head and neck.[20] S100 immunostaining was variably present within the neoplasm we describe, although comparison with other SCC or nonneoplastic oral mucosal epithelium from this species was unavailable.

In human cases of SCC, immunohistochemical staining for cytokeratin intermediary filaments CK 8/18 is a negative prognostic marker.[7] The expression of CK 8/18 has been associated with increased cellular motility, poor prognosis, and decreased cellular differentiation of SCC in a variety of sites and in other epithelial neoplasms.[24] In addition, cytokeratin 19 typically is expressed in the basal epithelial layer of the oral squamaous epithelium, and its suprabasilar expression has been correlated with premalignant transformation.[16] To our knowledge, the expression of these cytokeratin filaments in oral SCC of pigtail macaque has not previously been reported. Human papilloma virus 16 recently was implicated as the cause of a subset of human oropharyngeal SCC.[5] Only one other case in macaques (prior to the one we report here) has been examined for viral causes of oral SCC; both the previous and current cases were negative.[19]

Additional immunohistochemical stains that are reported to be involved in malignant behavior this type of carcinoma and other malignancies in humans, such as hypoxia-inducible factor-1 α, CD44 (a cancer stem cell marker), and IL6, reported to induce epithelial-mesenchymal transition involved in metastases, and other adhesion molecules such as β catenin and ε-cadherin were not investigated in this case due to the obvious morphologic criteria of malignancy and stromal invasion present in routine stains.

Antemortem diagnosis was not achieved in the presented case. Diagnosis of the pathologic process was attempted by using fine-needle aspiration, radiographs, hematology, clinical chemistry, physical exams, and progression of clinical signs. However, the aspirates were consistent with whole blood and did not reveal neoplastic cells; however, the aspirates did suggest that an infectious or inflammatory condition was unlikely, given the lack of purulent discharge, increased WBC count, and bacteria. An incisional biopsy likely would have been diagnostically valuable but was not obtained for multiple reasons. Biopsies, especially those involving bone, can be painful and require pain management by using opioids. In humans, fetal opioid exposure is well recognized potentially to result in

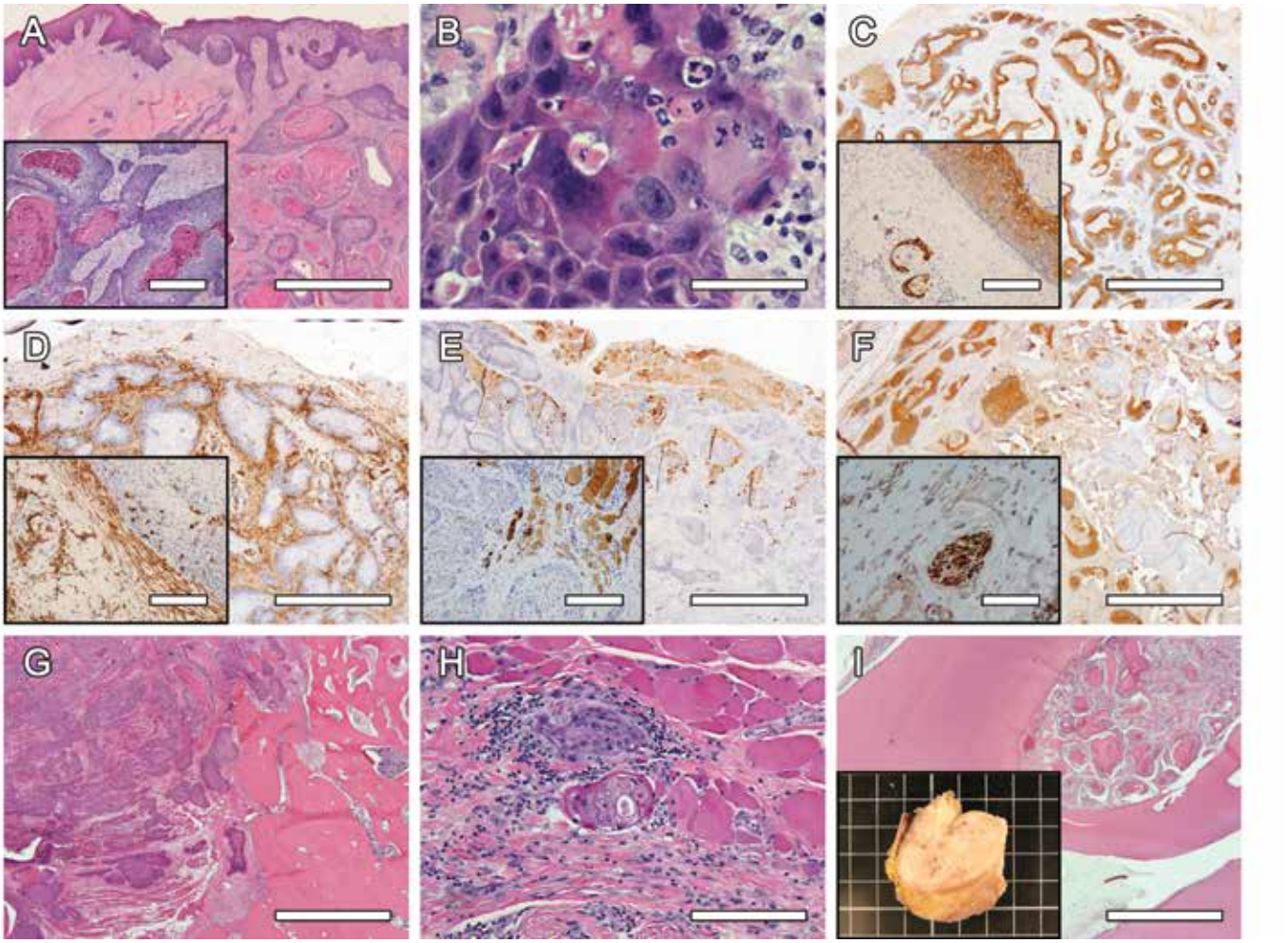

Figure 2. Histology and immunohistochemistry of SCC lesion. (A) Low-power photomicrograph (white bar, 1mm) of buccal mucosa. On the upper left, the squamous epithelium is acanthotic, whereas on the upper right the epithelium demonstrates neoplastic transformation. Neoplastic cells extend through the basement membrane into the deep submucosa and form packets, nests, and whorls, with central cores of eosinophilic, laminated keratin (keratin pearls). A higher-magnification inset (white bar, 250 µm) demonstrates islands of neoplastic squamous cells within a fibrovascular stroma. Central cores of laminated keratin contain apoptotic and necrotic cells. (B) High-magnification photomicrograph (white bar, 25 µm) of squamous neoplastic cells demonstrating the loss of intercellular bridges, lack of organization, anisokaryosis, anyisocytosis, dyskeratosis, and neutrophilic inflammation. (C) Low-power photomicrograph (white bar, 1 mm) of positive 3,3′-diaminobenzidine (DAB) immunohistochemical staining for the intermediate filament cytokeratin. Neoplastic cells are positive (brown) for this protein, whereas the fibrovascular stroma is negative (blue). The inset (white bar, 250 µm) illustrates the epithelial–stromal border, with 2 islands of cytokeratin-positive neoplastic cells within stromal tissues. (D) Low-power photomicrograph (white bar, 1 mm) of negative DAB immunohistochemical staining for the intermediate filament vimentin. Neoplastic cells are negative (blue) for this protein, whereas the fibrovascular stroma is positive (brown). The inset (white bar, 250 µm) illustrates the epithelial–stromal border with scattered positive stromal cells within neoplastic (negative) epithelilal cells. (E) Low-power photomicrograph of negative DAB immunohistochemical staining for desmin intermediate filament. Neoplastic cells and stroma are negative (blue) for this protein whereas overlying myocytes are positive (brown). The inset (white bar, 250 µm) illustrates the junction of muscle (upper right) and neoplastic tissue. (F) Low-power photomicrograph (white bar, 1 mm) of intermediate DAB immunohistochemical staining for calcium binding protein S100. Neoplastic cells are variably positive (brown) for this marker. The inset (white bar, 25 µm) illustrates a positive internal control; nerve fibers show positive (brown) staining. (G) Neoplastic cells invading and replacing mandibular bone (white bar, 1 mm). To the left, neoplastic cells and stroma abut bone (right) and invade marrow spaces. (H) Myocytes of the masseter muscle are replaced by neoplastic cells within fibrovascular stroma containing abundant inflammatory cells (white bar, 100 µm). (I) Photomicrograph (white bar, 1 mm) of the left maxillary premolar illustrating neoplastic invasion of alveolar bone and cementum; the dentin and pulp cavity are preserved. For orientation, the inset image illustrates the tissue origin (after fixation) and demonstrates the mandibular neoplastic tissue surrounding a premolar in cross section (grid, 5 mm).

neonatal abstinence syndrome.[12] In infants, this syndrome can be associated with tremors, increased muscle tone, seizures, hyperthermia, tachypnea, vomiting, and diarrhea, among other manifestations.[12] A premature macaque infant with signs similar to neonatal abstinence syndrome would have been very difficult to manage medically. In addition, pain from the biopsy procedure could have been sufficient to decrease the macaque's food intake. Anorexia could have had negative effects on the fetus and is one of many criteria for euthanasia. Furthermore, biopsy was not performed because the expected information was not likely to have changed the clinical management or prognosis of the problem.

As mentioned earlier, the current case was complicated by pregnancy. Pregnancy has not been associated with altering the natural progression of a tumor, despite causing immunologic alterations that may allow for tumor evasion of the immune system.[2] These alterations include depressed cellular immunity, the presence of human chorionic gonadotropin (an immunosuppressive substance), increased numbers of suppressor T lymphocytes, and the presence of a blocking antibody (IgG) to permit tolerance to antigenic tissue.[2] However, as in the current case, pregnancy can influence the clinical work-up, treatment options, and goals of therapy.[2] According to our macaque's clinical signs, her prognosis was poor. She underwent a pregnancy exam by a member of the veterinary staff at 3 mo prior to euthanasia. At that time, no abnormalities within the mouth were noted, demonstrating how rapid this lesion developed and progressed.

In conclusion, although neoplasms in macaques are relatively uncommon, SCC are one of the most common oral tumors. The current case represents the first report of an oral SCC in a pigtailed macaque, and SCC should be included in the differentials of oral masses particularly in older animals. In addition, this case demonstrates the difficulties associated with cancer treatment and diagnosis when the patient is pregnant.

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References

1. **Animal Welfare Act as Amended.** 2008. 7 USC §2131–2156.
2. **Barron WM, Lindheimer MD, Davison JM.** 2000. Medical disorders during pregnancy. St Louis (MO): Elsevier Mosby.
3. **Bennett BT, Abee CR, Hendrickson R, editors.** Nonhuman primates in biomedical research: diseases. San Diego (CA): Academic Press.
4. **Cianciolo RE, Hubbard GB.** 2005. A review of spontaneous neoplasia in baboons (*Papio* spp.). J Med Primatol **34:**51–66.
5. **Crozier E, Sumer BD.** 2010. Head and neck cancer. Med Clin North Am **94:**1031–1046.
6. **Ettinger SJ, Feldman EC.** 2004. Textbook of veterinary internal medicine, 6 ed, vol 2. St Louis (MO): Elsevier Health Sciences.
7. **Fillies T, Werkmeister R, Packeisen J, Brandt B, Morin P, Weingart D, Joos U, Buerger H.** 2006. Cytokeratin 8/18 expression indicates a poor prognosis in squamous cell carcinomas of the oral cavity. BMC Cancer **6:**10.
8. **Gardner DG.** 1996. Spontaneous squamous cell carcinoma of the oral region in domestic animals: a review and consideration of their relevance to human research. Oral Dis **2:**148–154.
9. **Haddad JL, Dick EJ, Guardado-Mendoza R, Hubbard GB.** 2009. Spontaneous squamous cell carcinoma in 13 baboons, a first report in a spider monkey, and a review in the nonhuman primate literature. J Med Primatol **38:**175–186.
10. **Hubbard GB, Wood HD, Fanton JW.** 1983. Squamous cell carcinoma with metastasis in a rhesus monkey (*Macaca mulatta*). Lab Anim Sci **33:**469–472.
11. **Institute for Laboratory Animal Research.** 1996. Guide for the care and use of laboratory animals. Washington (DC): National Academies Press.
12. **Jansson LM, Velez M, Harrow C.** 2009. The opioid-exposed newborn: assessment and pharmacologic management. J Opioid Manag **5:**47–55.
13. **Jean SM, Morales PR, Paul K, Garcia A.** 2011. Spontaneous primary squamous cell carcinoma of the lung in a rhesus macaque (*Macaca mulatta*). J Am Assoc Lab Anim Sci **50:**404–408.
14. **Kaspareit J, Friderichs-Gromoll S, Buse E, Haberman G.** 2007. Spontaneous neoplasms observed in cynomolgus monkeys (*Macaca fasicularis*) during a 15-year period. Exp Toxicol Pathol **59:**163–169.
15. **Kaspareit J, Friderichs-Gromoll S, Buse E, Karte R, Vogue F.** 2001. Spontaneous pulmonary neoplasms in cynomolgus mokeys (*Macaca fascicularis*)—a report of 2 cases. Exp Toxicol Pathol **53:**267–269.
16. **Lindberg K, Rheinwald JG.** 1989. Suprabasal 40-kd keratin (K19) expression as an immunohistologic marker of premalignancy in oral epithelium. Am J Pathol **134:**89–98.
17. **Morin ML, Renquist DM, Allen AM.** 1980. Squamous cell carcinoma with metastasis in a cynomolgus monkey (*Macaca fascicularis*). Lab Anim Sci **30:**110–112.
18. **McGavin MD, Zachary JF.** 2007. Pathologic basis of veterinary disease, 4th ed. St Lois (MO): Elsevier Mosby.
19. **Nakamura S, Sakakibara I, Ono F, Shibata S, Michishita M, Ishii Y, Kobayashi R, Takahashi K, Yoshikawa Y.** 2000. Squamous cell carcinoma of the oral cavity in an infant cynomolgus monkey. Exp Anim **49:**225–228.
20. **Sapkota D, Bruland O, Boe OE, Bakeer H, Elgindi OA, Vasstrand EN, Ibrahim SO.** 2008. Expression profile of the S100 gene family members in oral squamous cell carcinomas. J Oral Pathol Med **37:**607–615.
21. **Schmitz HC, Weishaupt D, Borel N, Padberg B, Bfirki K.** 2004. The use of ultrasound and computed tomography for the diagnosis of squamous cell carcinoma of the oesophago-cardial region of the stomach in a rhesus monkey. Lab Anim **38:**92–97.
22. **Simmons HA, Mattison JA.** 2011. The incidence of spontaneous neoplasm in 2 populations of captive rhesus macaques (*Macaca mulatta*). Antioxid Redox Signal **14:**221–227.
23. **Staheli JP, Ryan JT, Bruce AG, Boyce R, Rose TM.** 2009. Consensus-degenerate hybrid oligonucleotide primers (CODEHOPs) for the detection of novel viruses in nonhuman primates. Methods **49:**32–41.
24. **Weng YR, Cui Y, Feng JY.** 2012. Biological functions of cytokeratin 18 in cancer. Mol Cancer Res **10:**485–493.