Comparative Medicine
Copyright 2014
by the American Association for Laboratory Animal Science

Vol 64, No 1
February 2014
Pages 68–70

Case Report

Lip Salivary-Gland Hamartoma in a Cynomolgus Macaque (*Macaca fascicularis*)

Zaher A Radi[1,*] and Daniel G Morton[2]

An incidental, asymptomatic, well-circumscribed, solitary, submucosal nodular mass was detected on the mucosal surface of the inner lower lip in a female cynomolgus macaque (age, approximately 2.4 y) during a juvenile chronic toxicology study. Grossly, the nodule was soft with brown to tan discoloration and measured approximately 4 mm in diameter. Microscopically, the nodule was covered by normal stratified squamous epithelium and composed of well-circumscribed irregular lobules containing hyperplastic and normal-appearing mucinous salivary gland acini and ducts, which were separated by thick connective tissue septae. In light of the gross pathology and results of microscopic examination, salivary gland hamartoma was diagnosed. This lesion resembles adenomatoid hyperplasia of mucous salivary glands in humans, which is a rare nonneoplastic swelling. To our knowledge, this case description is the first report of a cynomolgus macaque with the rare entity of lip salivary gland hamartoma, which likely represents adenomatous hyperplasia in humans.

The term 'hamartoma' comes from the Greek words *hamartia* (defect or error) and *oma* (tumor-like growth) and was first introduced by Albrecht in 1904.[1] Hamartoma is a focal, benign, nonneoplastic developmental malformation or inborn error manifesting as an admixture of mature cells indigenous to the anatomic location of occurrence and that grows in a disorganized mass.[8] The histogenesis of hamartoma can involve any one of the germ cell layers (ectoderm, endoderm, or mesoderm). Intraoral hamartomas are rare. Intraoral salivary gland hamartoma has been reported to occur in humans[8] but not in veterinary species. No cases of lip salivary-gland hamartoma in cynomolgus monkeys, the most common nonhuman primate species used in toxicology studies in safety assessment of novel pharmaceutical therapeutic agents, have been reported previously. Here we report a case of lip salivary-gland hamartoma involving a cynomolgus macaque. The lesion in our case resembles adenomatoid hyperplasia of oral minor salivary glands in humans.[2,3,5,9]

Case Report

The affected animal was a 2.4-y-old, female cynomolgus macaque (*Macaca fascicularis*) from a 39-wk oral gavage juvenile toxicology Good Laboratory Practice (GLP) study that was conducted at a contract research organization in Munster, Germany. The organization is certified by the German authorities responsible for monitoring compliance with the Good Laboratory Practices and German Chemical Law and is AAALAC-accredited. Macaques in this study were housed in a temperature- (18 to 29 °C) and humidity- (30% to 70%) monitored environment. An automatic lighting system provided a 12:12-h diurnal cycle. The macaques were individually housed in stainless steel cages and fed daily with a commercial diet (Purina Certified Hi-Fiber Primate Diet, PMI Nutrition International, St Louis, MO). Fresh drinking water was provided free choice to all animals. Clinical and physical examinations, body weight assessment, and clinical hematology, biochemistry, and urinalysis were performed periodically throughout the conduct of the study. Throughout the study, no noteworthy problems (trauma, known penetrating injuries, and so forth) were reported in any of the macaques on study.

At study termination, the macaque of interest was euthanized by exanguination after intravenous administration of barbiturate-based anesthesia solution and necropsied. Multiple organs, including the lip mass, were collected, fixed in 10% neutral buffered formalin, routinely processed for hematoxylin and eosin staining, and evaluated by light microscopy.

In the macaque we report, all of the parameters assessed during the in-life portion of the study were within normal limits. At necropsy, a lip mass was located on the lower inner lip (Figure 1 A). The mass was well-circumscribed, solitary, and soft; had brown to tan discoloration; and measured approximately 4 mm in diameter. The mass was not noted (but likely was present) before the study; was small and not ulcerated; and easily could have been missed. There were no other incidents of gross pathology. Microscopically, the nodule was covered by normal, intact, stratified squamous epithelium and was composed of well-circumscribed, irregular lobules containing hyperplastic and normal-appearing mucinous salivary-gland acini and ducts, which were separated by thick connective tissue septae. There was no evidence of any inflammation (Figures 1 B and C). There were no other histopathologic lesions.

Received: 10 Jun 2013. Revision requested: 12 Aug 2013. Accepted: 19 Aug 2013.
[1]Pfizer Worldwide Research and Development, Drug Safety Research and Development, Andover, Massachusetts; [2]Pfizer Worldwide Research and Development, Drug Safety Research and Development, Cambridge, Massachusetts.
[*]Corresponding author. Email: Zaher.Radi@Pfizer.com

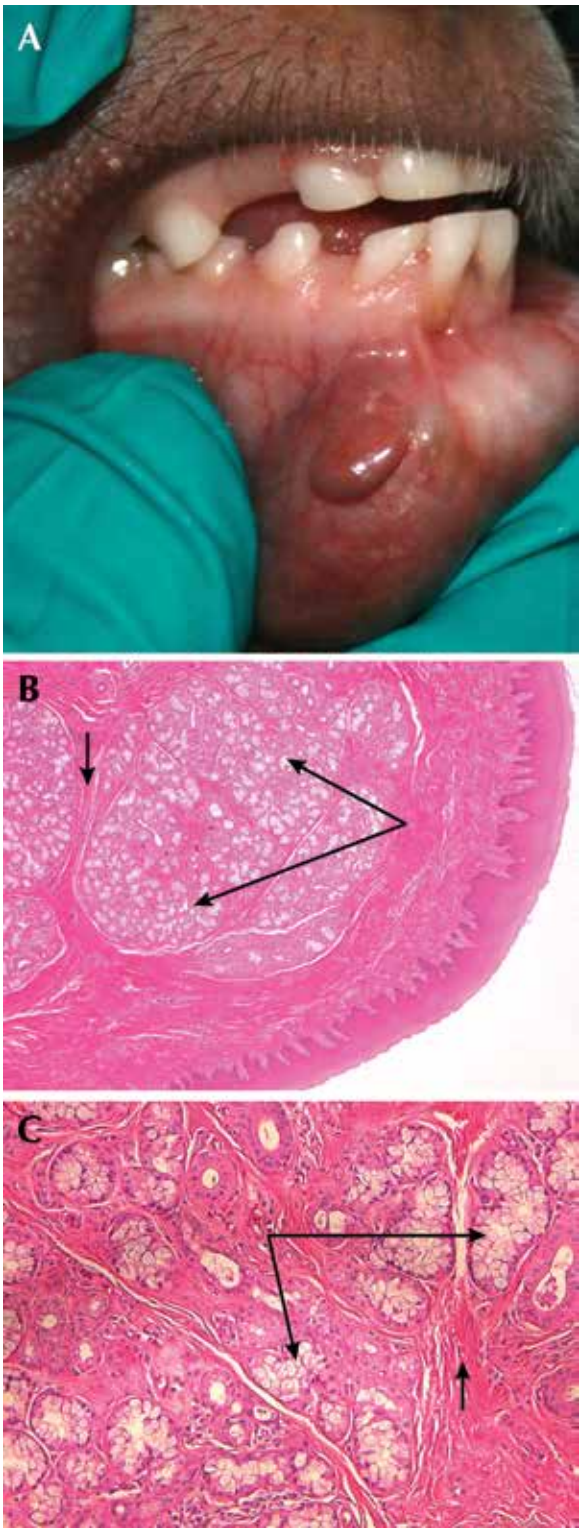

Figure 1. Female cynomolgus macaque (*Macaca fascicularis*). (A) Nodular mass on the lower inner lip. The mass (diameter, approximately 4 mm) was well-circumscribed, solitary, and soft with brown to tan discoloration. (B and C) Histopathology of the lip nodular mass. Note the normal stratified squamous surface epithelium and well-circumscribed, irregular lobules containing hyperplastic and normal-appearing mucinous salivary gland acini and ducts (long arrows) separated by thick connective tissue septae (short arrows). Magnification, 4× (B); 10× (C).

Discussion

In humans, a clinical entity called adenomatoid hyperplasia of oral minor salivary glands has been described.[2,3,5,9,10] Other names for the same clinical entity are benign minor salivary hypertrophy, salivary gland hyperplasia, and adenomatoid hyperplasia.[5] This clinical entity is rare and results in swelling of the oral minor salivary glands.[3] This benign, nonneoplastic, tumor-like lesion was first reported as hyperplasia of the local minor mucous salivary glands or the palate.[7]

The histopathologic features of adenomatoid hyperplasia in humans are hyperplastic salivary glands, which have normal or occasionally hyperplastic acinar morphology, and normal to hyperplastic or hyperkeratotic stratified squamous surface epithelium. Some cases have mild to moderate chronic submucosal inflammation or duct dilation.[3] The histopathologic features of the lip lesion in our case were: hyperplastic salivary glands, normal surface stratified squamous surface epithelium, and absence of inflammation. We have used the term salivary gland hamartoma instead of adenomatoid hyperplasia because we believe that hamartoma is more appropriate terminology for this lesion and because adenomatoid hyperplasia may connote a neoplastic or preneoplastic condition. The use of the term hamartoma clearly indicates that the lesion is composed of cells indigenous to the anatomic location of occurrence and is not neoplastic. Indeed, the term adenomatoid hyperplasia was adopted by colleagues who stated that this entity may represent either a reactive phenomenon or a hamartomatous proliferation.[2] The most commonly reported anatomic locations of adenomatoid hyperplasia have been the hard or soft palate, buccal mucosa, retromolar area, and upper lip.[2-6,9,10] However, a recent case of adenomatoid hyperplasia in the lower inner lip has been described.[10] The gross pathologic morphology and anatomic location of this recently reported case of adenomatoid hyperplasia are similar to those we noted in our macaque.

The pathogenesis of adenomatoid hyperplasia is unclear, and it has been considered an idiopathic condition. However, chronic local trauma has been suggested to play a role in its pathogenesis.[3,5] Some have suggested that adenomatoid hyperplasia represents hamartoma because both occur most commonly in the 4th through 6th decades.[4,5] Because salivary gland hamartomas are benign, complete surgical excision of the lesion is curative, and there is no recurrence of the lesion after adequate surgical excision.[5,7] The lesion we noted in our monkey was not present at the beginning of the study, and there was no history of trauma. Therefore, developmental pathogenesis (that is, hamartoma) was likely in our macaque. The salivary-gland hamartoma in this animal was a spontaneous and incidental finding.

In veterinary medicine and among laboratory animal species, no cases of lip salivary-gland hamartoma in cynomolgus macaques used in toxicology studies have previously been reported. Lip lesions in juvenile and young cynomolgus monkeys generally are very rare in pharmaceutical safety assessment studies. This case we present here represents the first description of a lip salivary-gland hamartoma in a cynomolgus monkey. This incidental lesion should not be mistaken with other nonneoplastic and neoplastic lesions or test-article–related lesions.

References

1. **Albrecht E.** 1904. Ueber hamartoma. Verh Dtsch Ges Pathol **7:**153–157.

2. **Arafat A, Brannon RB, Ellis GL.** 1981. Adenomatoid hyperplasia of mucous salivary glands. Oral Surg Oral Med Oral Pathol **52:**51–55.
3. **Barrett AW, Speight PM.** 1995. Adenomatoid hyperplasia of oral minor salivary glands. Oral Surg Oral Med Oral Pathol Oral Radiol Endod **79:**482–487.
4. **Brannon RB, Houston GD, Meader CL.** 1985. Adenomatoid hyperplasia of mucous salivary glands: a case involving the retromolar area. Oral Surg Oral Med Oral Pathol **60:**188–190.
5. **Buchner A, Merrell PW, Carpenter WM, Leider AS.** 1991. Adenomatoid hyperplasia of minor salivary glands. Oral Surg Oral Med Oral Pathol **71:**583–587.
6. **Devildos LR, Langlois CC.** 1976. Minor salivary gland lesion presenting clinically as tumor. Oral Surg Oral Med Oral Pathol **41:**657–659.
7. **Giansanti JS, Baker GO, Waldron CA.** 1971. Intraoral, mucinous, minor salivary gland lesions presenting clinically as tumors. Oral Surg Oral Med Oral Pathol **32:**918–922.
8. **Stricker TP, Kumar V.** 2010. Neoplasia, p 261. In: Kumar V, Abbas AK, Nelson F, Aster J, editors. Robbins and Cotran pathologic basis of disease, 8th ed. Philadelphia (PA): Elsevier.
9. **Petri WH 3rd, Carr RF, Kahn CS.** 1993. Adenomatoid hyperplasia of the palate. J Oral Maxillofac Surg **51:**310–311.
10. **Sharma GK, Sharma M, Vanaki SS.** 2011. Adenomatoid hyperplasia of lower lip. Dent Res J (Isfahan) **8:**226–228.