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Lacrimal Gland Myoepithelioma in a Rhesus Macaque (*Macaca mulatta*)

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An 18-year-old rhesus macaque (*Macaca mulatta*) developed ptosis of the left upper eyelid due to a mass that had first been observed 10 years previously. The 11 × 7 × 7-mm mass was surgically excised, and the ptosis resolved after 5 days. Histologic examination of the mass revealed two confluent cell populations. Most cells were spindle-shaped and were arranged in loose fascicles. Smaller numbers of cells had squamous differentiation. The spindle-shaped cells expressed smooth muscle actin. Cells with squamous differentiation did not express smooth muscle actin, but did, along with around half of the spindle-shaped cells, express pan-cytokeratin. On the basis of histologic and immunohistochemical findings, the mass was diagnosed as myoepithelioma. The neoplasm most likely originated from the palpebral lobe of the lacrimal gland, although accessory lacrimal gland origin could not be excluded. Recurrence of the neoplasm has not been observed 6 months after surgery.

The lacrimal glands produce an aqueous solution that constitutes the middle layer of the tear film (16). To the authors' knowledge, lacrimal gland neoplasia has not been reported in a non-human primate (1). Lacrimal gland neoplasia is considered rare in humans and has seldom been reported in animals (3).

Myoepitheliomas are epithelial tumors derived from contractile cells in secretory glands (6). They are considered rare in all species except mice (18). Myoepithelioma in the mammary gland of a cynomolgus monkey has been reported (20). We describe the clinical presentation, surgical removal, and histologic appearance of lacrimal gland myoepithelioma in a rhesus macaque.

Case Report

In 1993, an 8-year-old, 9.0-kg, male rhesus macaque (*Macaca mulatta*) was introduced into the primate facility of the Medical College of Georgia. The captive-born macaque had previously been used as a breeding animal. While in quarantine, the macaque was observed to have a small mass in the left upper eyelid close to the lateral canthus. At the end of the quarantine period, the macaque was individually housed in a stainless steel cage and was used for cognition experiments. The animal was fed commercial food (Teklad Global 20% Protein Primate Diet, Harlan Teklad, Indianapolis, Ind.), and water was available via an automatic watering system. The diet was supplemented with fruit and foraging mix. Husbandry and maintenance of the macaque colony in this AAALAC, International-approved facility was in accordance with recommendations listed in the *Guide for the Care and Use of Laboratory Animals*. All experimental use of this animal was reviewed and approved by the Institutional Animal Care and Use Committee.

Semiannual physical examination included a complete blood count, serum biochemical analysis, and intradermal tuberculin testing. The clinical history of this animal was unremarkable except for the left eyelid mass, the size of which was observed to slowly increase over a period of 10 years. At that time, ptosis of the upper eyelid developed (Fig. 1), and it was decided to excise the mass.

Figure 1. An 18-year-old rhesus macaque with ptosis and a mass in the left eyelid.

One hour prior to surgery, the animal was pre-anesthetized with ketamine HCl (10 mg/kg of body weight, i.m.), and general anesthesia was induced and maintained with isoflurane. Standard aseptic preparation was applied to the skin over the left upper eyelid and brow. Xylocaine with epinephrine was injected subcutaneously to enhance intraoperative hemostasis. A horizontal skin incision was made by use of a scalpel, just below the

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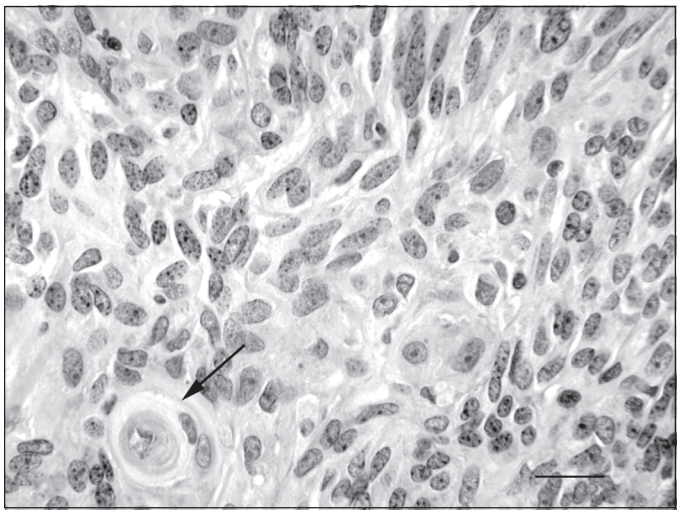

Figure 2. Photomicrograph of a section of the lacrimal gland myoepithelioma. Notice that most cells are short, spindle shaped, and arranged in fascicles. The arrow indicates an area of squamous differentiation. H&E stain; bar = 13 μm.

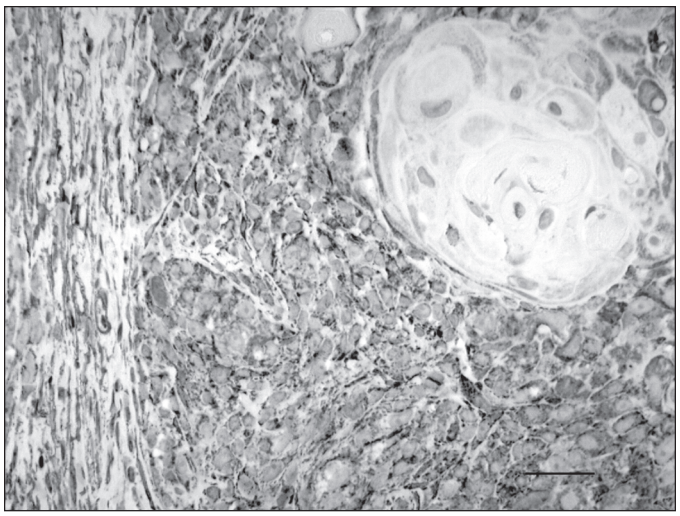

Figure 3. Photomicrograph of a section of the lacrimal gland myoepithelioma. Notice diffuse expression of smooth muscle actin by the short spindle-shaped cells. Cells with squamous differentiation (top right corner) do not react with smooth muscle actin antibodies. Avidin-biotin-peroxidase complex system and Gill's hematoxylin. Bar = 20 μm.

superior lateral orbital rim. Sharp and blunt dissection was used to dissect and isolate the lesion, which extended close to the palpebral conjunctiva. The upper lid retractor was identified, and care was taken to avoid damage to this structure. The mass was then excised, and the incision was closed with buried and cutaneous 5-0 Vicryl (Ethicon, Somerville, N.J.) sutures. After unremarkable recovery from anesthesia, ptosis continued for 5 days before resolving. Tumor recurrence has not been observed in the 6 months following the surgery.

The excised mass was fixed in buffered 10% formalin and was processed in routine manner for histologic examination. Immunohistochemical analysis was performed using commercially available antibodies to smooth muscle actin (Dako Corporation, Carpinteria, Calif.) and pan-cytokeratin (Biogenex, San Ramon, Calif.). The avidin-biotin-peroxidase complex system (Vector Laboratories, Burlingame, Calif.) was used to visualize all immune reactions.

Histologic examination of the mass revealed an $11 \times 7 \times 7$-mm proliferation of cells. The neoplasm was encapsulated, with minimal penetration of the capsule by the neoplastic cells. However, the capsule was not visible in some tissue sections and complete excision could not be confirmed histologically. The neoplastic cells were partitioned into multiple small lobules by a well developed fibrovascular stroma. Two confluent populations of neoplastic cells were visible within the neoplasm. Approximately 80% of the cells were short, spindle-shaped, and arranged within broad fascicles and wide loose bundles (Fig. 2). The neoplastic cells contained a bland, cigar-shaped nucleus, with an inconspicuous single nucleolus. The cytoplasm was variable, most cells having moderate quantities of eosinophilic material and smaller numbers of cells containing large quantities of clear cytoplasm. One mitosis per ten high-power fields was visible in the spindle cell population.

The second cell population constituted around 20% of the neoplasm and consisted of nests of epithelial cells that were randomly scattered throughout the neoplasm. The cell nests varied in size from 10 cells to 0.08 mm in diameter. These cells had squamous differentiation and were large and polygonal. Most contained a large, round nucleus; however, approximately 30% of the squamous cells had either a pyknotic nucleus or no visible nucleus. The cytoplasm was extensive and varied from pale and slightly granular to brightly eosinophilic. Approximately 30% of the squamous cells contained small brightly eosinophilic keratohyalin granules in the perinuclear area. Mitotic figures were rare in this cell population. The larger nests of squamous differentiation rarely had a central cavity that contained keratin debris and hemorrhage. Adjacent to the neoplasm was a small compressed glandular structure that was continuous with the neoplastic proliferation of cells. This structure consisted of well-formed glandular acini and ducts. The acini contained large foamy cells and, on the basis of location of the neoplasm, this structure was interpreted to be part of the palpebral lobe of the lacrimal gland.

Immunohistochemical staining revealed intense cytoplasmic reactivity to anti-smooth muscle actin antibodies throughout the spindle-shaped cell population (Fig. 3). Cells in the squamous cell population did not react to the antibody. Use of antibodies against pan-cytokeratin revealed diffuse intense cytoplasmic reactivity in cells with squamous differentiation (Fig. 4). Additionally, approximately 50% of the spindle-shaped cells also had mild to moderate cytoplasmic positivity to this antibody. Cells in the acini and ducts of the lacrimal gland reacted with antibodies against pan-cytokeratin, but not smooth muscle actin. Small numbers of small, spindle-shaped cells in the gland expressed smooth muscle actin. It is uncertain whether these cells represented normal glandular myoepithelial cells or neoplastic cells that had infiltrated the gland.

Discussion

Secretory glands such as salivary, sweat, mammary, and lacrimal glands contain two populations of epithelial cells (4). Luminal epithelial cells form the ducts and the acini of the glands. The second population of epithelial cells is located between the luminal epithelial cells and the basement membrane (4). These myoepithelial cells contain actin, are contractile, and squeeze secretions out of the gland (4).

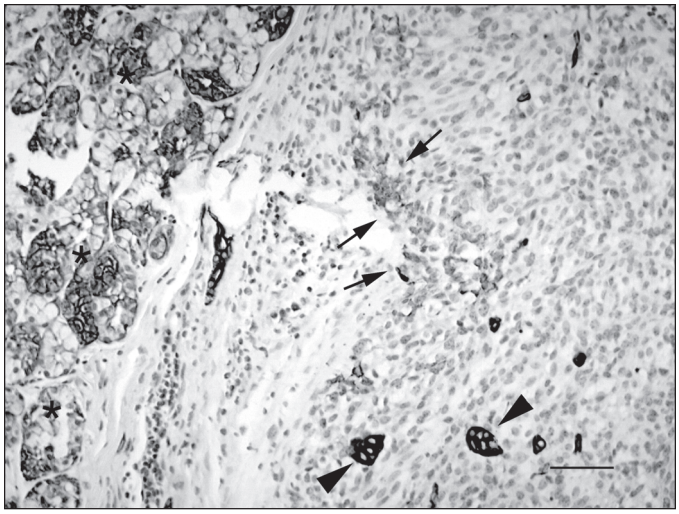

Figure 4. Photomicrograph of a section of the lacrimal gland myoepithelioma. Small numbers of cells, typically within nests, react strongly positive with pan-cytokeratin antibodies (arrowheads). Less-intense staining is visible within some spindle-shaped cells (arrows). Residual lacrimal gland is indicated by an "*" on the left side of the photomicrograph. Avidin-biotin-peroxidase complex system and Gill's hematoxylin. Bar = 40 μm.

Benign epithelial tumors that develop in secretory glands are classified according to the population of cells from which the tumor is derived. If the neoplasm consists of luminal epithelial cells, the tumor is classified as an adenoma (6). Conversely, if the neoplasm consists solely of a proliferation of myoepithelial cells, it is classified as a myoepithelioma (6). If differentiation toward both myoepithelial and luminal epithelial cells is present, the tumor is classified as a pleomorphic adenoma (6). Due to the presence of more than one type of differentiation, pleomorphic adenomas are also called mixed tumors (6).

Myoepithelial origin of the currently described neoplasm was suggested by the dual expression of pan-cytokeratin and smooth muscle actin by most of the neoplastic cells. Although squamous differentiation was visible, ductular or acinar structures were not visible within the neoplasm. Because evidence of luminal epithelial cell differentiation was not observed, this tumor was classified as myoepithelioma rather than pleomorphic adenoma. Squamous differentiation in a mammary gland myoepithelioma that developed in a cynomolgus monkey also has been reported (20).

The glandular tissue that was associated with the tumor was histologically consistent with salivary or lacrimal gland. In humans and rhesus macaques, the lacrimal gland is divided into orbital and palpebral lobes (16, 19). The orbital lobe of the lacrimal gland is not clinically palpable and is situated in the uppermost lateral part of the orbit. Enlargement of this lobe causes lateral displacement, proptosis, and compression of the eyeball (3). The palpebral lobe of the lacrimal gland extends into the lateral margin of the upper eyelid. Tumors of the palpebral lobe present as swelling of the upper eyelid, without visible displacement of the globe (19). Palpebral gland neoplasms constitute up to 17% of lacrimal gland neoplasms in humans (19). Due to the tumor location, myoepithelioma of the palpebral lobe of the lacrimal gland was diagnosed. However, accessory lacrimal glands are scattered throughout the eyelids (17), and a neoplasm derived from these cannot be excluded in this animal.

Lacrimal gland neoplasia is considered rare in humans (3). Lacrimal gland lesions account for between 5 and 13% of all biopsied orbit masses (15). However, in a recent survey of 142 lacrimal gland biopsies, neoplasia accounted for only 31% of the lesions (15). The remaining lesions consisted of inflammation (63%) and dacryoceles (6%) (15). Of the neoplasms that develop in the lacrimal glands, estimates of the proportion that are of epithelial origin vary between 16% (15) and 50% (13). Estimates of the proportion of epithelial lacrimal gland tumors that are benign vary between 50% (13) and 70% (15). Pleomorphic adenomas are the most common benign epithelial tumor of the lacrimal gland (15). Fewer than five reported cases of lacrimal gland myoepitheliomas are found in human literature (5).

Lacrimal gland neoplasia in animals also is rare. Of laboratory rodents, two carcinomas of lacrimal gland origin in rats have been reported (7). Spontaneous mouse lacrimal gland neoplasms were not identified in a literature review that was done in 1996 (10). Lacrimal gland neoplasms in dogs are considered rare, and most primary tumors are adenocarcinomas (11). Pleomorphic adenoma of the lacrimal gland in a dog has been reported (9). To the authors' knowledge, myoepithelioma of the lacrimal gland has not been reported in a non-human species.

The recommended treatment for benign epithelial lacrimal gland neoplasms in humans is surgical excision (14). Complete excision is curative; however, tumors have been found to have a high rate of recurrence if neoplastic cells are dispersed into adjacent tissues during biopsy or removal (14). Additionally, malignant behavior is often observed in tumors that recur following surgery (12). Therefore, biopsy of benign epithelial tumors of the lacrimal gland is contraindicated (14). An algorithm has been proposed to determine whether the lesion is likely to be benign (and thus should be surgically removed without biopsy) or malignant (and should then be biopsied prior to the formation of a treatment plan) (14). This algorithm considers the duration the mass has been present, whether or not the neoplasm causes pain, and whether or not there is loss of vision (14). In the animal of this report, the mass had been present for at least 10 years and did not appear to cause pain, suggesting benign biological behavior. A review of the literature did not reveal prognostic information for lacrimal gland neoplasms in animals.

Myoepitheliomas are rare in humans and animals. In humans, they most commonly develop, in order of decreasing frequency, in the skin, salivary glands, and breast (2). Malignant myoepithelioma in the mammary gland of a cynomolgus monkey has been reported (20). Myoepitheliomas as components of canine mixed mammary tumors have been reported (8). Retrospective survey of 12,000 animals revealed 142 myoepitheliomas in inbred laboratory mice (18). These tumors developed in areas adjacent to salivary, mammary, clitoral, preputial, and harderian glands (18).

Due to the presence of neoplastic cells adjacent to the tissue margins, complete excision of the tumor in the animal of this report could not be confirmed histologically. Therefore, recurrence was considered possible. However, 6 months after surgery was performed, there was no evidence of tumor recurrence and excision appears to have been curative.

In conclusion, to the authors' knowledge, this is the first report of lacrimal gland neoplasia in a non-human primate. Additionally, this is the second myoepithelioma that has been reported in a non-human primate (20). Unlike the previously reported non-

human primate myoepithelioma that subsequently underwent metastasis (20), the currently described tumor had benign biological behavior. In humans, biopsy of benign lacrimal gland epithelial tumors is not recommended due to the risk of embedding neoplastic cells within surrounding tissues (14). If tumors of this type behave similarly in humans and non-human primates, it may be advisable to completely excise any slow-growing, painless mass that is observed in the orbital area without performing prior biopsy.

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