

Co-existence of mixed meibomian gland and ductal adenoma with an apocrine sweat gland cyst in a dog: histological and immunohistochemical analyses

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Article Info	Abstract
Article history: Received: 27 July 2021 Accepted: 26 October 2021 Available online: 15 June 2022	A 14-year-old female Shih Tzu was presented with conjunctivitis, keratitis, an enlarged mass located on the left lower eyelid and a large subcutaneous cyst in the temporal region. The hematological and biochemical analyses revealed no significant issues. The mass and the cyst were taken from the base with 1.50 cm of the underlying tissue. On histological examination, the mass was made up of adenoid arrangements of sebocytes and basaloid reserve cells with low to moderate mitotic activity of basaloid cells. In addition, a large number of meibomian ducts with marked infiltration of mononuclear inflammatory cells and melanin pigment were observed in the ductal part of the tumor. The cyst was lined by a simple cuboid-like epithelium with no eosinophilic cuticular lining. Immunohistochemical staining of the mass with CK14 showed positive reaction in the neoplastic basaloid reserve cells and adipocytes; but, not with CK18 and vimentin. Unlike, the luminal cells of the cyst were stained with CK18. The co-existence of mixed meibomian gland and ductal adenoma with an apocrine sweat gland cyst was diagnosed based on the clinical, histological and immunohistochemical findings.
Keywords: Apocrine sweat gland cyst Immunohistochemistry Lower eyelid Meibomian adenoma Meibomian ductal adenoma	

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Introduction

Meibomian (tarsal) glands of the eyelids are a type of sebaceous gland that their secretions provide nutrients to the cornea. They are found on the tarsal plate and responsible for forming the lipid layer over the thin pre-corneal film of tear.¹ Most of the tumors localized on the eyelids are either benign melanoma and papilloma or tumors of meibomian glands.^{1,2} Meibomian tumors appear as small and slow growing masses being most commonly seen in elderly dogs and rarely in other species.² Compared with meibomian gland adenomas, other types of meibomian tumors including meibomian epithelioma, meibomian adenocarcinoma and meibomian ductal adenomas are uncommon.^{3,4}

The case being presented here might be of interest because it reports the co-existence of mixed meibomian gland and ductal adenoma with a large apocrine sweat gland cyst in a Shih Tzu dog.

Case Description

A 15-year-old female Shih Tzu weighting 7.00 Kg was presented with a four-month history of eye problems. Conjunctival congestion, conjunctivitis, cataract and keratitis were detected on physical and ophthalmic examinations. A firm brown-black multi-lobulated cauliflower-like mass arising from the left lower eyelid margin was visible (Fig. 1A). Additionally, a large and slowly growing soft cyst, 3.00 cm in diameter, containing an abundant clear and watery fluid, with a hyperemic wall was observed on the temporal region of the same aspect (Fig. 1B). Complete blood count and biochemical tests (some criteria such as alanine transaminase, aspartate transaminase and alkaline phosphatase levels, cholesterol, calcium, and phosphorous) along with urinalysis were carried out. The examined values all were within normal range. The entire mass and cyst with overlying skin were surgically excised under sterile condition and fixed in

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10.00% neutral buffered formalin. The tissue samples were processed routinely in a paraffin wax, sectioned at 5- μ m thickness and stained with Hematoxylin and Eosin (H&E). In addition, immunohistochemical study on the mass was performed for CK14, CK18 and vimentin antibodies (Dako, Glostrup, Denmark; for all markers). Nor local neither distant metastasis was revealed after one year of the surgery.

On histological examination, adenoid arrangements of sebaceous cells together with basaloid reserve cells were separated by a fibrous stroma (Fig. 2A). The basaloid reserve cells differentiating into sebocytes were evident and they had scant eosinophilic cytoplasm and uniform round to ovoid nuclei with one to two small nucleoli (Figs. 2B and 2C). These cells showed moderate mitotic activity with two to three mitotic figures per each high-power field with no pleomorphism (Fig. 2C). The large and mature sebocytes exhibited an abundant pale foamy and vacuolated cytoplasm with a central nucleus containing one or two small nucleoli (Fig. 2C). These cells showed no mitotic activity. Numerous inflammatory cells including lymphocytes, plasma cells, macrophages and occasionally multi-nucleated giant cells were infiltrated into the fibrous connective tissue surrounding the adenoid masses (Fig. 2B). In some areas of the tumor, moderate amount of melanin pigment was also seen (Figs. 2A and 2B).

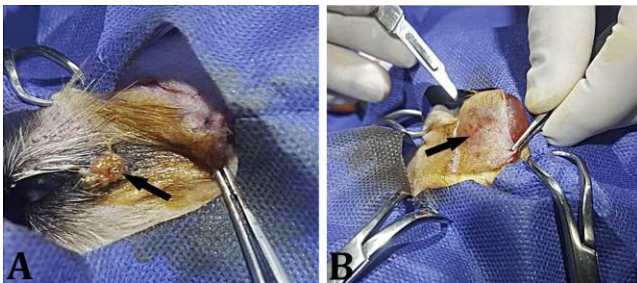


Fig. 1. **A)** A well-circumscribed cauliflower multi-lobulated mass on the left lower eyelid of a 14-year-old female Shih Tzu (arrow). **B)** Note the large cutaneous cyst of apocrine sweat gland with a hyperemic wall on the left temporal region (arrow).

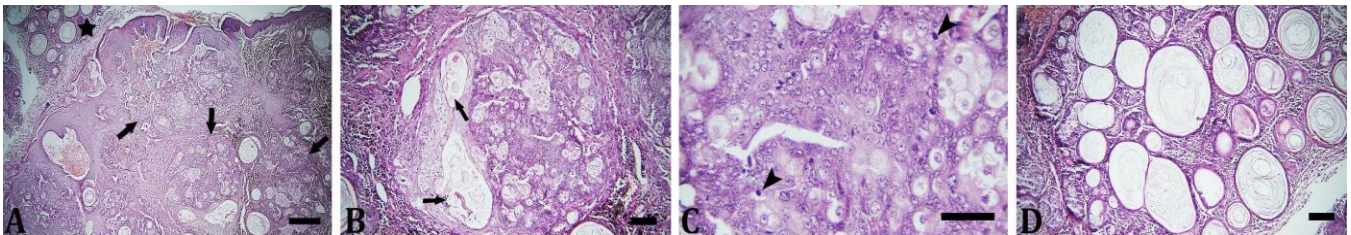


Fig. 2. Representative photomicrographs of the meibomian adenoma and ductal adenoma (compound meibomian adenoma) on the left lower eyelid. **A)** The mass was consisted of well-defined adenoid arrangements separated by thin fibrous connective tissue (arrows). Note ductal structures surrounded by inflammatory cells on the left top (asterisk). There is a melanin pigmentation on the right and congestion and hemorrhage (H&E, scale bar = 300 μ m). **B)** Gland islets consisted of mature sebocytes and undifferentiated basaloid reserve cells surrounded by mononuclear inflammatory cells together with melanin pigment on the right corner. Note the dilated meibomian ducts containing eosinophilic sebum/keratin (arrows). Note moderate to abundant clear cytoplasm of mature sebocytes (H&E, scale bar = 100 μ m). **C)** Basaloid cells have ovoid to round nuclei with small nucleoli showing several mitotic figures (arrowheads), (H&E, scale bar = 50 μ m). **D)** Ductal component of the tumor is composed of numerous ducts with varying sizes being filled with variable keratin contents and surrounded by the stroma infiltrated by mononuclear inflammatory cells (H&E, scale bar = 100 μ m).

Interestingly, a large number of variably sized ducts containing eosinophilic sebum and/or keratin being lined by simple squamous epithelium were detected in addition to the adenoid arrangements (Figs. 2A and 2D). Infiltration of the considerable mononuclear inflammatory cells was visible around the ducts (Fig. 2D).

Regarding the cyst on the temporal region, the overlying epidermis was intact and the sebaceous glands were normal. Apocrine sweat glands were slightly dilated (Fig. 3A) and a large cyst lined by a thin layer of low cuboidal/squamous-like epithelium, most likely originated from the glands, with a hyperemic wall was clearly visible (Figs. 3A and 3B). The inner surface of the cyst was not corrugated and had no eosinophilic cuticular lining. The cyst contents were lost during tissue processing and thereby, it was empty without any keratin/sebum or other materials in microscopic examination.

In order to reveal the origin of the neoplastic cells from basaloid reserve cells of sebaceous glands, immunohistochemical analyses were conducted using antibodies for CK14 as the sebocyte and basaloid marker, CK18 as a luminal cell marker as well as vimentin. The neoplastic cells indicated a strong positive staining for CK14 (Fig. 4A); whereas, there were no stainable cells for CK18 and vimentin (Figs. 4B and 4C).

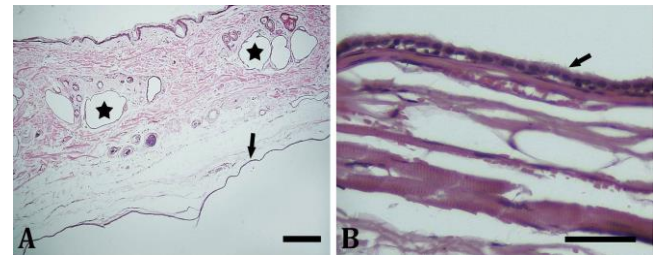


Fig. 3. **A)** Slightly dilated sweat glands (asterisks) in dermis with a large apocrine sweat gland duct cyst (arrow), (H&E, scale bar = 300 μ m). **B)** The large cyst is lined by a simple cuboidal epithelium changed to stratified squamous in some parts of the cyst wall due to the pressure of fluid (arrow). Note hyperemia and hemorrhage around the wall of the cyst (H&E, scale bar = 50 μ m).

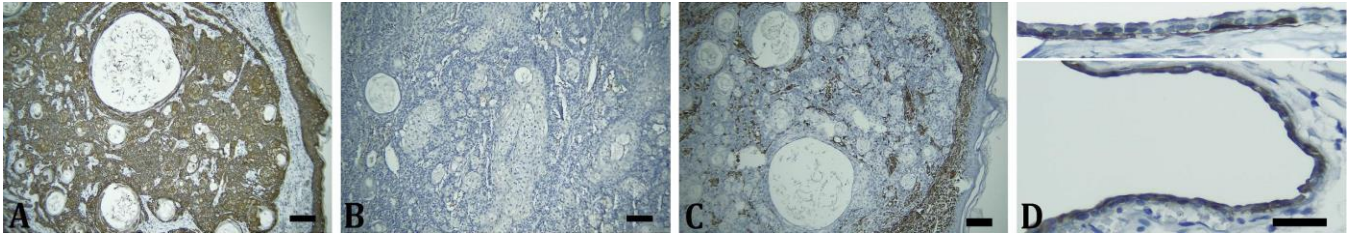


Fig. 4. **A)** Positive immunohistochemical staining for CK14 (Scale bar = 100 μ m). **B)** Negative immunohistochemical staining for CK18 in neoplastic basaloid cells and adipocytosis (Scale bar = 100 μ m). **C)** Vimentin is positive for inflammatory cells, the fibrous stroma around the neoplastic cells and the sebaceous ducts; whereas, it is not stained for the neoplastic cells (Scale bar = 100 μ m). **D)** Epithelial cells lining the cyst are slightly and heavily positive for CK14 (the top section) and CK18 (the bottom section), respectively (Scale bar = 50 μ m).

Immunohistochemistry for vimentin was positive only for inflammatory cells and collagen stroma around the adenoid mass (Fig. 4C). This expression pattern was inverse concerning the cyst found on the temporal region (Fig. 4D); so that, the luminal cells were strongly and slightly positive for CK18 and CK14, respectively. Based on clinical, gross and microscopic characterizations of the mass and cyst, the present case was diagnosed as a mixed meibomian gland and ductal adenoma concurrent with a large apocrine sweat gland cyst.

Discussion

One of the most commonly reported neoplasms of the eyelid in dogs are meibomian gland tumors.^{3,5} They are histologically classified as adenomas, ductal adenomas, epithelioma and carcinomas.^{4,6} The tumors all originate from undifferentiated basal cells of the meibomian glands. They have a similar clinical appearance as slow-growing, pink, gray, brown or black masses spreading from the meibomian gland orifice and occasionally erupting the palpebral conjunctiva.⁴

According to a study carried out by Wang *et al.*,⁷ benign eyelid tumors (67.20%) were significantly more widespread than malignant tumors (7.60%) and non-tumor masses (25.20%) in a sample of 119 eyelid masses in 118 dogs. They found meibomian epithelioma as the most common tumor followed by meibomian adenoma and meibomian carcinoma, with no occurrence of meibomian ductal adenoma. Additionally, upper eyelid neoplasms (61.30%) were significantly more common than lower ones (37.80%) in 119 masses.⁷ Since there are more meibomian glands in the upper eyelid of dogs, it is probably more vulnerable to neoplastic changes than the lower eyelid.^{2,4,8} Conversely, the tumor in the present study and also meibomian tumors in large animals were initiated from the lower eyelid.^{2,3}

No sex and breed predispositions have been reported.⁹ However, in the research undertaken by Wang *et al.*,⁷ mixed breed dogs (14.40%), Labrador Retrievers (11.00%) and Toy Poodles (9.30%) as well as Golden Retrievers and Shih Tzus (8.50%) were the most frequently affected breed and they have reported a higher

prevalence of eyelid masses in males than female dogs. The case being reported here was Shih Tzu and female.

Our findings were consistent with the histological changes reported in the literature.^{1,2,4,10} Meibomian adenomas are characterized by lobules composed of mature sebocytes and lipid-laden cells with basaloid reserve cells.^{6,10} These tumors should be differentiated from carcinomas considering mitoses in sebocytes as well as high cellular and nuclear pleomorphism in carcinomas.⁴ No pleomorphism was observed in the neoplastic cells/nuclei of the present case. Meibomian ductal adenomas, on the other side, are composed of a large number of varying-sized ducts with few sebocytes or basaloid cells.⁴ In addition, histological analysis of the neoplastic mass revealed varying amounts of melanin pigment. In support of our findings, pigmentation has been identified as a common finding in meibomian tumors.² On the contrary, lack of pigmentation has been also reported in the meibomian adenoma in a calf and meibomian epithelioma in a horse.^{3,8}

Immunohistochemical analyses for CK14 and CK18 have been proposed for differentiating sebaceous tumors from other adnexal luminal neoplasms.⁶ From this point of view, it has been demonstrated that normal and neoplastic sebocytes and thus, sebaceous tumors are positive for CK14; but, not for CK18.^{6,11} As a result, strong positive staining for CK14 and negative expression for CK18 in the present study could confirm that the tumor cells are originated from basaloid reverse cells and not from the apocrine luminal cells. In contrast, the epithelial cells lining the temporal cyst were stained heavily for CK18 representing their apocrine origin. It has been reported that CK18 is expressed in normal apocrine sweat glands.^{6,11}

Considering the meibomian gland and ductal adenoma diagnosed in this case, it was initially thought that the large cyst found on the temporal region is a sebaceous duct cyst. Despite the clear and watery contents of the cyst in the present study, sebaceous duct cysts contain a white and milky fluid. Furthermore, keratin/sebum-containing cystic lesions lined by a thin layer of stratified squamous epithelium with an undulating/corrugated surface eosinophilic cuticle and basal cell palisading are referred

as sebaceous duct cysts.^{10,12} On the other hand, the sebaceous glands located in the dermis were normal and there was no evidence regarding hyperplasia. On the contrary, the present cyst was lined by a cuboidal to squamous epithelium without a typical corrugated eosinophilic cuticle on the inner surface. Moreover, the apocrine glands were slightly dilated and therefore, it was more likely to be an apocrine sweat gland cyst. Apocrine cysts are well-defined cysts with a single cuboidal epithelium and no visible contents in tissue sections, varying in size from few millimeters to several centimeters in diameter.¹⁰

In conclusion, although meibomian adenoma is common in dogs, the readers may be interested in the case as it represents meibomian gland adenoma and meibomian ductal adenoma of the lower eyelid as well as an apocrine sweat gland cyst, all at the same time in a dog and so, it seems extremely rare from this point of view. To treat the eyelid and periorbital neoplastic masses particularly benign tumors of meibomian glands and ducts, complete surgical excision of the tumor can be curative. The prognosis of surgical tumor is usually good with no recurrence or complications. However, cryotherapy and chemotherapy are also effective.⁷

Acknowledgments

The authors are truly grateful to Mr. Mohammad Nejad for his technical assistance.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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