

## Scientific Report

# Coincidence of meibomian adenoma and squamous cell carcinoma in the upper eyelid of a sheep: histopathological and immunohistochemical studies

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## Summary

This report is related to a female 7-year-old crossbreed sheep whose right eye had been protruded and swelling of upper eyelid was observed. Routine enucleating was performed. Histopathological evaluation of eyelid revealed coincidence of two kinds of neoplasms. The first part was composed of multiple lobules of sebocytes, which were detected as meibomian adenoma. The second section included infiltrating islands of neoplastic squamous epithelium extending through the basal lamina of the epithelium with keratin pearls and was noted as grade I squamous cell carcinoma. Immunohistochemical study of cytokeratin showed positive reaction in both kinds of neoplastic cells. This is a rare case of meibomian adenoma in sheep with squamous cell carcinoma coincidence.

**Key words:** Meibomian adenoma, Squamous cell carcinoma, Sheep, Immunohistochemistry

## Introduction

Glands of the eyelid consist of sebaceous glands such as tarsal (meibomian) and Zeis glands which open to hair follicles and also moll glands that have a modified structure of sweat gland (Dellman and Eurell, 1998). Meibomian glands contribute a lipid component to the tear film, which aids in the dispersal of the aqueous component of the tear film and helps prevent evaporation (Junqueira *et al.*, 1998). Sebaceous glands give rise to sebaceous gland hyperplasia, sebaceous adenoma, sebaceous epithelioma and sebaceous carcinoma. Modified sebaceous glands, meibomian glands, which give rise to meibomian gland adenomas, epitheliomas, and carcinomas that are histologically identical to the corresponding sebaceous gland lesions and will not be described separately; meibomian adenoma is the most common tumor of the canine eyelid and in

any other species is infrequent to rare (Goldschmidt and Hendrick, 2002; Wilcock, 2007).

Squamous cell carcinoma is probably the most important primary ocular neoplasm of domestic animals. It arises from the epithelium of the limbus, third eyelid or eyelids (Sironi *et al.*, 1999). Squamous cell carcinoma in sheep occurs more frequently in areas deprived of wool and pigmentation, such as eyes (Ladds and Entwistle, 1977), ears (Ladds and Entwistle, 1977), nose (Ladds and Entwistle, 1977), forehead (Tafti and Meimandi Parizi, 1998), perineum (Lagadic *et al.*, 1982), vulva and mucocutaneous junctions (Lagadic *et al.*, 1982). In human, conjunctival squamous cell carcinoma is rare with multifactorial etiology but exposure to solar ultraviolet radiation is considered as a major cause (Sironi *et al.*, 1999).

To the best of the author's knowledge, this is a rare case report of meibomian

adenoma in eyelid of sheep and also coincidence of this tumor with squamous cell carcinoma with histopathology and immunohistochemistry characteristics in veterinary literature.

## Case presentation

A female 7-year-old crossbreed sheep suffering from right eye protrusion for 3 months, referred to the veterinary hospital of Shahid Chamran University of Ahvaz. Swelling of upper eyelid was observed and overlying scale crusts were obvious. Routine enucleating was performed and for histopathologic and immunohistochemical studies, samples of masses were sent to the Department of Pathology. Appropriate samples were fixed in 10% neutral-buffered formalin and routine process in pathology lab was done and haematoxylin and eosin stained slides were studied. For immunohistochemical study, Monoclonal Mouse Anti-Human Cytokeratin (AE1/AE3; clone AE1/AE3, Dako, Denmark) as primary antibody and Polyclonal Goat Anti-Mouse Immunoglobulin (Dako, Denmark) as secondary antibody were used.

## Results

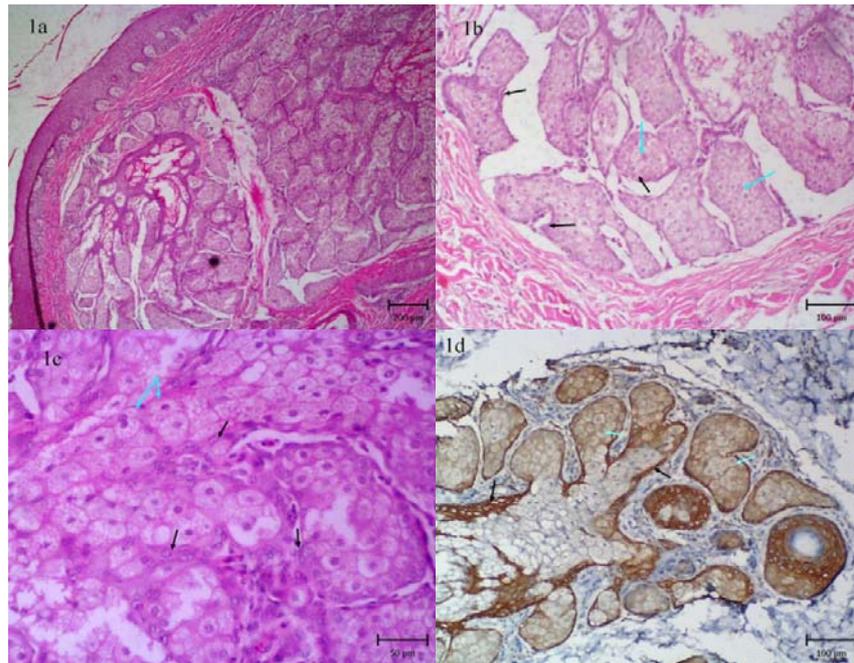
Histopathological evaluation of eyelid revealed coincidence of two kinds of neoplasms. The first part was composed of multiple lobules of sebocytes, which were separated by connective tissues (Fig. 1a). They were of various sizes and the central part of each lobule showed large and mature sebocytes and periphery displaying relatively small, undifferentiated germinative basaloid cells (Fig. 1b). The mature sebocytes contain pale staining, foamy and vacuolated cytoplasm with central and crenated, hyperchromatic nuclei (Fig. 1c). The smaller basaloid cells revealed round to oval vesicular nuclei and basophilic cytoplasm (Fig. 1c). Eosinophilic materials, which resemble keratin and sebum were seen within lobules. The first parts were identified as meibomian adenoma. The second section was identified by proliferation of malignant keratinocytes,

which were beyond the basal lamina of epidermis (Fig. 2a). Infiltrating keratinocytes formed multiple islets of neoplastic cells and there were eosinophilic materials in the center of the islets, which were identified as keratin pearls and intercellular bridge between keratinocytes was obvious (Figs. 2b, c). According to the mentioned characteristics, grade I squamous cell carcinoma was diagnosed. Also, infiltration of neutrophils and plasma cells, fibroplasias, acanthosis and pseudoepitheliomatous hyperplasia were seen. Immunohistochemical results of cytokeratin staining showed two reactions for sebocytes. The sebocytes, which were located in the periphery of the lobules and basaloid cells, showed dark brown as positive reaction but cells situated in the center of the lobules showed weak staining to negative reaction (Fig. 1d). Squamous cell illustrated intense brown coloration in cytoplasm and it was stronger in mature keratinocytes (Fig. 2d).

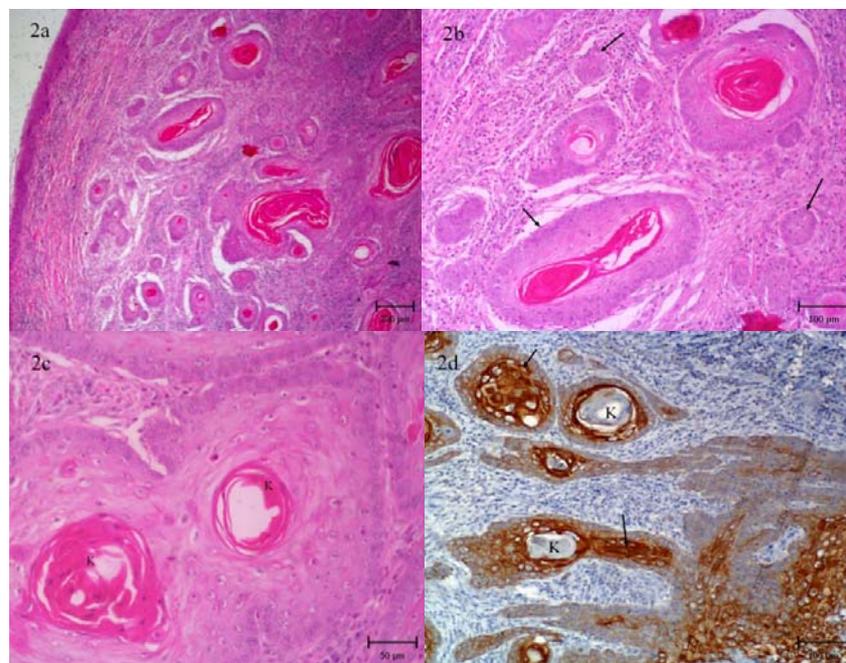
## Discussion

Meibomian adenoma is a benign tumor of the tarsal glands with exact counterpart of sebaceous adenomas seen elsewhere in skin and consists of different size of lobular structures, well-differentiated sebaceous cells of regular distribution among lobules and undifferentiated basal cells surrounding both of these structures. In this case, proliferated sebocytes which were separated by connective tissues developed multiple lobules. Eosinophilic materials resembling keratin and sebum were seen within lobules. These findings had similarities with other changes reported for meibomian adenoma in literature (Yuksel *et al.*, 2005). The infiltration of inflammatory cells that was seen may be related to obstruction of the lipid secretion which may induce gland rupture and subsequent release of lipid glandular secretion into the eyelid tissues, inducing a moderate inflammatory response.

Immunohistochemical study for cytokeratin showed two types of cells reactions in meibomian adenoma. The peripheral cellular components, the basal and ductal cells, showed positive reaction,



**Fig. 1: Meibomian adenoma. a:** Well circumscribed dermal lobulated tumor (H&E, bar = 200  $\mu$ m). **b:** Lobules are composed of sebocytes with various sizes (H&E, bar = 100  $\mu$ m). **c:** Part of Fig. 1b with high magnification. They show large and mature sebocytes in central (blue arrows) and periphery displaying relative small, undifferentiated basaloid cells (black arrows). Note the foamy and vacuolated cytoplasm of sebocytes (H&E, bar = 50  $\mu$ m). **d:** Immunostaining for cytokeratin. Note the positive cytokeratin expression, which is clear by brown cytoplasm staining. Intense coloration of basaloid cells (black arrow) and weak to negative staining of sebocytes (blue arrows) are clear (immunohistochemistry staining, haematoxylin counterstain, bar = 100  $\mu$ m)



**Fig. 2: Squamous cell carcinoma. a:** Invasion of the dermis by abnormal epidermal cells (H&E, bar = 200  $\mu$ m). **b:** Note the multiple islets of tumor cells in dermal area (black arrows) (H&E, bar = 100  $\mu$ m). **c:** Part of picture B with high magnification, note the keratin pearls (K) in squamous cell carcinoma from intraepithelial keratinization and keratinocytes with pleomorphism and intercellular junctions (H&E, bar = 50  $\mu$ m). **d:** Immunostaining for cytokeratin. Note the positive cytokeratin expression of invasive cells (black arrows) which have brown cytoplasm staining (immunohistochemistry staining, haematoxylin counterstain, bar = 100  $\mu$ m)

whereas central foamy cells illustrated negative reaction with the antibody panel used. Johnson *et al.* (1999) reported that normal sebaceous glands and all sebaceous neoplasms show a dimorphic cell population in immunohistochemical studies which is probably due to fat entity of central cells with foamy cytoplasm, and is in agreement with this case findings in meibomian adenoma.

Meibomian adenomas are reported to be more frequent in aged dogs and cats when compared to other domestic animal species and also females have a higher number of adenomas compared to males (Yuksel *et al.*, 2005). In bovine the most common eyelid tumors that are reported are squamous cell carcinomas with age dependence (Lagadic *et al.*, 1982). In the present study, the sheep was 7-year-old and female, thus it is in agreement with other reports.

In researches about ovine squamous cell carcinoma, different etiology has been reported such as genetic factors, mutations of p53 tumor suppressor gene, papilloma virus with ovine papillomas and UVB-induced (Lagadic *et al.*, 1982; Sironi *et al.*, 1999). In the present study the affected sheep belonged to Ahvaz city (in the south of Iran) which has a warm climate with solar radiation, so this is probably UVB-induced.

The exact etiology of sebaceous gland tumors is not known. It is supposed that hormonal dysfunction may play a significant role in development of these kinds of tumors (Rungsipipat, 2003). Also, in human oncology there is a hypothesis for these kinds of tumors. Muir-Torre syndrome is a rare autosomal dominant genodermatosis, first described in 1967, characterized by the presence of sebaceous tumors and an internal malignancy in the absence of other predisposing factors and the presence of sebaceous tumors warrants a search for an internal malignancy (Akhtar *et al.*, 1999). So in this case, incidence of squamous cell carcinoma may be a predisposed condition for meibomian adenoma. This is a rare case of meibomian adenoma in sheep with

squamous cell carcinoma coincidence.

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