

Conjunctival Papillomas and Corneal Squamous Cell Carcinomas after long-term Cyclosporine Treatment in four Brachycephalic Dogs with Chronic Keratitis

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Introduction:

Immunosuppressive medication with cyclosporine is an efficacious therapy for many ophthalmic inflammatory conditions in dogs. Cyclosporine inhibits T cell activity and in consequence their normal immunresponse. Conjunctival or corneal papillomas occur often after papillomavirus infection, especially in young dogs. Rarely canine corneal squamous cell carcinomas are developing spontaneously and usually originating from conjunctiva. In humans, the association between chronic inflammation and neoplasia and between immunosuppressive therapy and cancer development is well documented. In contrast only few reports establish an association in veterinary medicine. The aim of this study was to describe similar cases of chronic keratitis, topical immunosuppressive treatment and development of a corneal or conjunctival tumor in four brachycephalic dogs.

Literature:
 1. Biese C, Sorenson J, Dubielzig R.R. and Hayes A. Corneal squamous cell carcinoma in a Border Collie. *Veterinary Ophthalmology* (2008) 11, 1, 55-58.
 2. Dreyfus J, Schmitt C. S. and Dubielzig R. R. Superficial corneal squamous cell carcinoma occurring in dogs with chronic keratitis. *Veterinary Ophthalmology* (2011) 14, 3, 161-168.
 3. Morikawa-Ferreira F., Melli-Krupel M., Muzalon P. and Truppel J. Corneal squamous cell carcinoma in a dog: a case report. *Veterinary Ophthalmology* (2008) 11, 4, 269-272.

Materials and Methods:

- Case 1: French bulldog, male spayed, 9 years.
- Case 2: English bulldog, male spayed, 11 years.
- Case 3: Pug dog, male, 11 years.
- Case 4: English bulldog, female, 9 years.

All of these four dogs belong to a brachycephalic breed with a clinical history of chronic keratoconjunctivitis. They all received a topical immunosuppressive treatment with Cyclosporine for more than a year and developed a mass on conjunctiva or cornea consequently. The masses, and in one case additionally the whole globe, were surgically removed and processed for histopathology. An in-situ-hybridisation was performed to exclude a papillomavirus origin of the tumours.



Fig. 1: Case 1: French bulldog with a small mass at the margin of the nictitating membrane.



Fig. 2: Case 1: Papillary growth of conjunctival epithelium, HE, 40x.



Fig. 3: Case 3: Pug dog with an axial and nasal mass on the surface of the cornea.

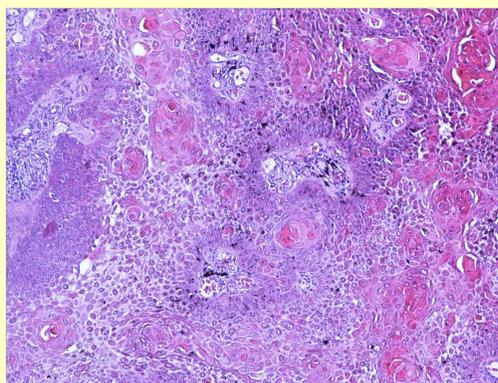


Fig. 4: Case 3: Islands and trabeculae of basaloid epithelial cells, partially pigmented, with progression to keratinized cells and keratin pearls, 100x.



Fig. 5: Case 4: English bulldog with an extensive and elevated central mass on corneal surface.



Fig. 6: Case 4: Marked thickening of epithelium with papillary growth and no invasion into corneal stroma, HE, 200x.

Results:

Histopathologically, the masses of two dogs (case 1 and 2) consisted of finger-like projections of conjunctival epithelium with uniform nuclei and no increased number of mitosis, pointing to a papilloma (Fig. 2). The two other masses (case 3 and 4) showed a verrucous growth characterized by broad papillary proliferations and trabeculae of hyperplastic epithelium. The nuclei showed moderate anisokaryosis, mitotic activity above basal cell layer, multifocally areas with keratinisation but no invasion into corneal stroma (case 4), indicating a squamous cell carcinoma (in situ). In all four lesions a papillomavirus involvement could be excluded by in-situ-hybridisation.

Discussion:

The results support the presumption of an association between chronic ophthalmic inflammatory conditions, the topical immunosuppressive therapy and tumour development. Papillomavirus origin was excluded. The brachycephalic breed appears to be an additional risk factor. As therapy, superficial keratectomy with complete excision of the mass is recommended. The risk of metastasis appears to be low.