

Papilloma and sebaceous gland hyperplasia of the lacrimal caruncle: a case report

Maria Miura-Karasawa¹
Hiroshi Toshida¹
Toshihiko Ohta¹
Akira Murakami²

¹Department of Ophthalmology,
Juntendo University Shizuoka
Hospital, Izunokuni, Shizuoka, Japan;

²Department of Ophthalmology,
Juntendo University School of
Medicine, Tokyo, Japan

Objective: To report a case of coincidence of sebaceous gland hyperplasia and papilloma with detection of human papillomavirus-51 in the apical portion by in situ hybridization.

Case presentation: A 75-year-old man noted discomfort at the inner canthus of his left eye when he blinked. A tumor of the lacrimal caruncle was identified and resected. The base of the tumor had a smooth surface and was whitish. In addition, a “navel-like structure” was seen, and the findings strongly suggested sebaceous gland hyperplasia of the lacrimal caruncle. The apical portion of the tumor was a papillomatous lesion. Histological examination of the resected tumor led to a diagnosis of sebaceous gland hyperplasia. Human papillomavirus-51 was detected in the apical portion by in situ hybridization. Based on these results, the final diagnosis was sebaceous gland hyperplasia with papilloma. No recurrence of either tumor has been observed up to 3 years postoperatively.

Conclusion: This might be the first report of a case of coincidence of sebaceous gland hyperplasia and papilloma, even though the association between these two lesions was unclear, including which developed first.

Keywords: lacrimal caruncle, sebaceous gland hyperplasia, papilloma, human papilloma virus, HPV-51

Introduction

The lacrimal caruncle is located at the inner canthus of the eye, and its non-keratinized epithelium resembles the conjunctival epithelium. It contains hair follicles, sebaceous glands, sweat glands, and other tissues that are present in the skin, as well as accessory lacrimal glands.¹ Therefore, any of the tumors that can arise in the skin, conjunctiva, and lacrimal gland may potentially develop at the lacrimal caruncle. It remains controversial whether tumors arising at the lacrimal caruncle should be classified as eyelid tumors or conjunctival tumors, but these lesions are generally classified according to the tissue of origin if histopathological examination is performed.

Conjunctival tumors are relatively uncommon.² In particular, conjunctival tumors occurring at the lacrimal caruncle are rare, and have generally been reported to comprise only 4%–5% of all conjunctival tumors.^{3–5} In the previous reports, nevoid and papillomatous tumors account for the majority of these lesions.^{2–6} On the other hand, tumors of the lacrimal caruncle classified as eyelid tumors include benign neoplasms such as sebaceous gland hyperplasia, cystic tumor, and nevus, as well as malignant neoplasms like sebaceous gland carcinoma. Accordingly, careful differentiation between benign and malignant tumors arising at this site is very important.^{5–7} According to our previous

Correspondence: Hiroshi Toshida
Department of Ophthalmology, Juntendo
University Shizuoka Hospital, Izunokuni,
Shizuoka, 410-2295, Japan
Tel +81 55 948 3111
Fax +81 55 948 3351
Email toshida@juntendo.ac.jp

study, 102 out of 118 eyelid tumors (86.4%) were benign and only 16 tumors (13.6%) were malignant.⁸ In addition, only four tumors (3.4%) were found at the inner canthus of the eye, all of which were benign, including two nevi and two epidermal cysts. These reports suggest that tumors originating from the sebaceous glands are very rare.

Here, we report a patient who underwent curative resection of sebaceous gland hyperplasia at the lacrimal caruncle that was associated with a papillomatous component in which human papillomavirus (HPV) was detected.

The institutional review board at Juntendo University Shizuoka Hospital fully approved our case study. The approval number was RIN-568. The authors have also obtained a written informed consent form from the patient to be involved in the case study following “Ethical Guidelines for Medical and Health Research Involving Human Subjects” established by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare.¹⁴ The tenets of the Declaration of Helsinki were followed, and written informed consent was obtained from patient before the patient received the surgery.

Case presentation

A 75-year-old man visited a local ophthalmologist because of discomfort and a foreign body sensation due to a mass at the inner canthus of his left eye. He had first noticed the mass about 10 years ago, and it had enlarged recently. He was referred to the Ophthalmology Department of Juntendo University Shizuoka Hospital for detailed examination and treatment. His past medical history included hypertension and prostatic hyperplasia, while the family history was not contributory. At the first visit, corrected vision was 1.2 in both eyes using a Snellen chart. There were no significant abnormalities of eye position or eye movements. Slit-lamp microscopy revealed a tumor at the lacrimal caruncle of the left eye. The mass measured ~2×2.5 mm. Its base had a smooth surface and was whitish with dilated capillaries (Figure 1A). These findings were suggestive of an enlarged lacrimal caruncle. However, the apical portion of the tumor showed mild hyperemia and had a papilloma-like appearance. After inverting the protruding portion of the tumor, which appeared to be growing from the palpebral fissure, with a cotton swab, a “navel-like structure” was observed near the center of the lesion (Figure 1B). In addition, early cataracts were detected in both eyes, but there were no significant changes of the fundus and the intraocular pressure was normal.

Based on these findings, a benign tumor of the inner canthus was suspected, such as sebaceous gland hyperplasia. To alleviate the patient’s symptoms, complete resection of this

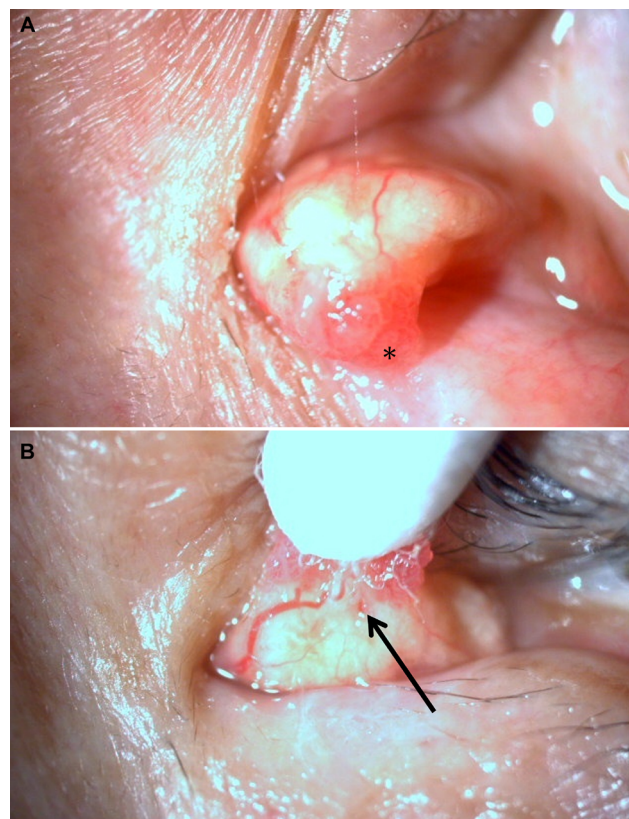


Figure 1 Clinical appearance of the tumor of the lacrimal caruncle at the first visit. **Notes:** (A) Outside of the tumor. It appeared smooth surface and was whitish with dilated capillaries. In addition, the apical portion of the tumor had a papilloma-like appearance with mild hyperemia (*). (B) Backside of the tumor. The “navel-like structure” was observed near the center of the lesion in the backside (arrow).

lesion was performed 2 weeks after the first visit. Surgery was done under topical instillation of 0.4% oxybuprocaine hydrochloride ophthalmic solution (Benoxi®; Santen pharmaceutical Co. Ltd, Osaka, Japan) and local anesthesia by injection of 1% lidocaine (Xylocaine®; Aspen Japan, Tokyo, Japan) into the bulbar conjunctiva along the circumference of the lesion. The tumor arose from the conjunctival tissue at the lacrimal caruncle, but did not involve the eyelid or the punctum. Complete resection of the tumor, including a region that seemed to contain the sebaceous glands of the lacrimal caruncle, led to removal of not only the whitish sebaceous glands but also the caruncle itself. The defect was closed with a single suture through the bulbar conjunctival epithelium using 8-0 Polysorb™ thread (Covidien, NY, USA). There were no adhesions between the tumor and surrounding tissues. The patient’s symptoms, including a foreign body sensation and ocular discomfort, gradually subsided after surgery.

Histopathological findings

The resected tumor was subjected to histopathological examination after staining with H&E (Figure 2). At the base of the tumor, sebaceous gland hyperplasia was observed

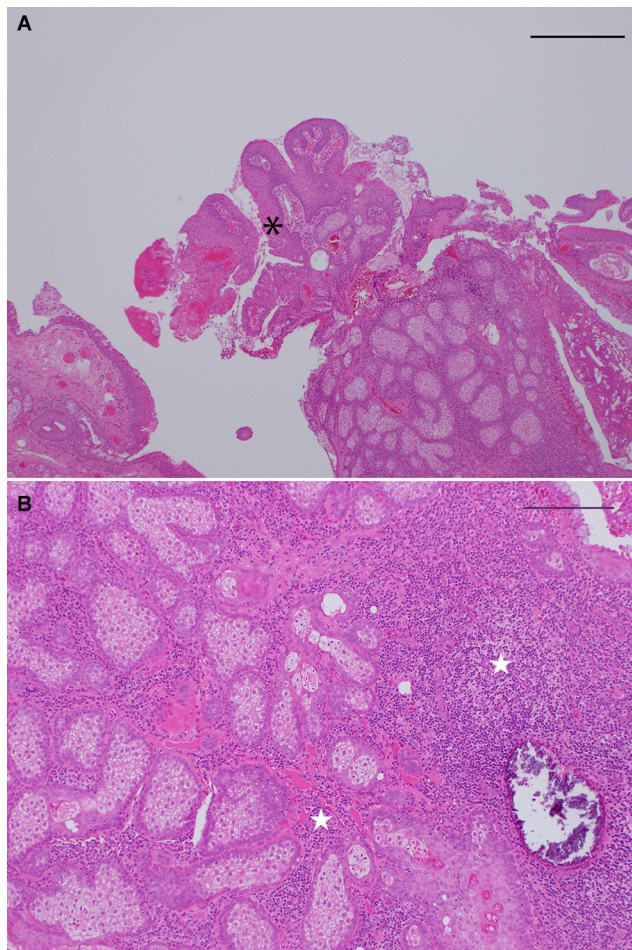


Figure 2 Histopathological findings on staining with H&E.

Notes: (A) Appearance of the papilloma and sebaceous gland hyperplasia regions. The apical portion of the tumor resembled a conjunctival papilloma and papillary proliferation of the epithelium was seen (*). At the base of the tumor, sebaceous gland hyperplasia was observed. Bar=1 mm. (B) High-magnification image of the sebaceous gland hyperplasia region. The sebaceous gland hyperplasia was observed involving adipocytes with moderate inflammatory cell infiltration (☆). Bar=400 µm.

involving adipocytes and there was moderate inflammatory cell infiltration. The apical portion of the tumor resembled a conjunctival papilloma and papillary proliferation of the epithelium was seen, although its surface was smooth. The tumor parenchyma consisted of a pedunculated mass formed by highly vascular fibrous connective tissue, and the boundary between the lesion and the epithelium was clear.

Analysis of HPV in the papillomatous component

In order to investigate possible HPV infection, we have employed the genotyping procedure that allows the simultaneous detection of 16 high- and low-risk genital HPV types by multiplex PCR in a single reaction tube analyzed by GeneticLab Co., Ltd. (Sapporo, Japan). The apical portion of the tumor with papilloma-like features was subjected to

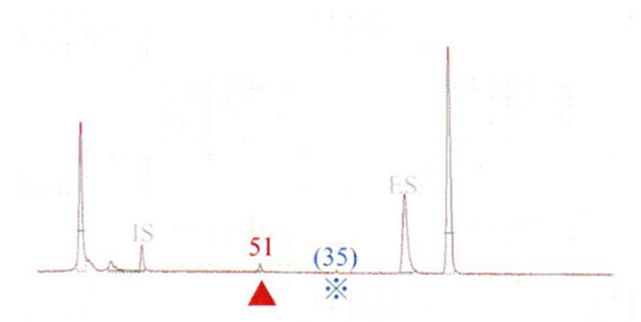


Figure 3 Result of the in situ hybridization for HPV positivity.

Notes: HPV-51 was detected in the apical portion (triangle). IS: Aminolevulinic acid synthase I was amplified for the multiplex PCR. ES for multiplex PCR: DNA fragments derived from *Brevundimonas diminuta* cloned to plasmid pCRII-TOPO (Invitrogen Corporation, Carlsbad, CA, USA) were added to the PCR mixtures along with external plasmid-specific primers. HPV-35 was negligible (*).

Abbreviations: ES, external positive standard; HPV, human papillomavirus; IS, internal positive standard..

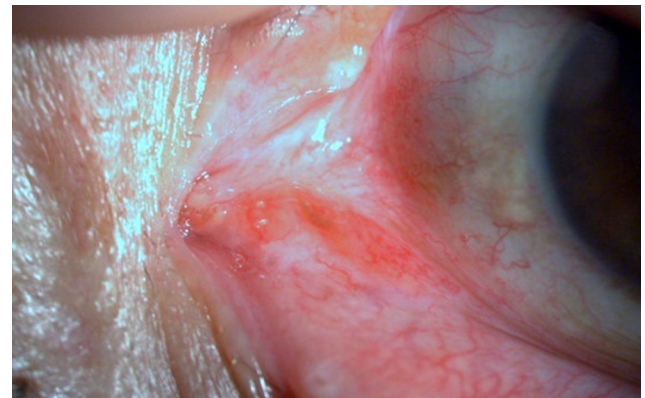


Figure 4 Clinical appearance after resection of the tumor.

Notes: There has been no recurrence of the tumor up to 3 years postoperatively.

in situ hybridization using an HPV DNA probe.⁹ The assay targeted HPV types -6, -11, -16, -18, -30, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, and -66, among which only HPV-51 was detected (Figure 3).

Clinical course

There has been no recurrence of the tumor up to 2.5 years postoperatively (Figure 4).

Informed written consent was obtained from the patient for publication of case details and images.

Discussion

The role of the lacrimal caruncle is not fully understood. Since it contains abundant sebaceous glands and has hair follicles, both a secretory function and removal of foreign substances from the eye have been suggested as possible roles. In humans, the semilunar fold of the bulbar conjunctiva lies closer to the eyeball than the lacrimal caruncle. It has been suggested that

the semilunar fold is the vestigial human organ corresponding to the nictitating membrane. Most primates have a semilunar fold, while many other animal species have a nictitating membrane at the inner canthus of the eye. The nictitating membrane is sometimes referred to as the third eyelid, and is supposedly responsible for protecting the surface of the eyeball and eliminating foreign substances. Among mammals, rodents and carnivores have a Harderian gland, which is a sebaceous gland located within the orbit behind the nictitating membrane, but this gland only exists in some primates.¹⁰ The Harderian gland is the only gland that secretes lipids via exocytosis. Its functions presumably vary among mammals, eg, protecting the surface of the eye in aquatic mammals or acting as a sebaceous gland or attractant gland in rodents and lagomorphs.¹¹ Some authors have suggested that the lacrimal caruncle is the human remnant of the Harderian gland, based on both anatomical and histological considerations.

The lacrimal caruncle has been suggested to exhibit characteristics of both mucosal membrane and skin, and it contains sebaceous glands and accessory lacrimal glands. As with tumors elsewhere, it is very important to distinguish between benign and malignant tumors of the lacrimal caruncle due to the difference in the prognosis. Adenocarcinoma is the most common malignant tumor of the lacrimal caruncle. Macroscopically, adenocarcinoma has an irregular surface and a mottled appearance with a yellow to yellowish-white color. The tumor of the present patient had the following macroscopic features: 1) origin from the lacrimal caruncle, 2) smooth whitish surface with a striated pattern, and 3) a “navel-like structure” that was probably a sebaceous gland duct.^{6,12} These findings were all characteristics of sebaceous gland hyperplasia. In particular, careful examination of the back of the tumor led to detection of the navel-like structure, which helped to exclude the possibility of a malignancy that would disrupt such structures and strongly suggested a diagnosis of sebaceous gland hyperplasia. In fact, subsequent histopathological examination revealed hyperplasia of sebaceous glands with adipocytes and infiltration of inflammatory cells, confirming the diagnosis of sebaceous gland hyperplasia. An adenocarcinoma would have shown nuclear enlargement, bulky fat vacuoles, and dedifferentiation, unlike the present findings.

It is also important to assess the characteristics of a tumor when it is grasped with forceps during surgery. If the lesion is an adenocarcinoma, it will be hemorrhagic, and prolapse of small granular tumors is commonly observed. In contrast, the present tumor was firm and could be grasped easily even with toothless forceps. Such findings are characteristics of

benign tumors, especially sebaceous gland hyperplasia. In short, all of the findings in the present case were consistent with a benign tumor, including the preoperative macroscopic appearance, histopathological features, and operative findings.

According to Luthra et al,⁶ the nevus is the most common tumor of the lacrimal caruncle, followed by papilloma and sebaceous gland hyperplasia. In the present patient with sebaceous gland hyperplasia, the apical portion of the tumor had the macroscopic appearance of a papilloma, and HPV-51 was detected by in situ hybridization. Conjunctival papillomas are generally known to be related to HPV-6, -11, -16, and -18.¹¹ However, Galor et al¹³ recently detected HPV-51 in 2 out of 27 conjunctival papillomas, suggesting that this subtype also causes such papillomas. Based on these reports, it seems that the papillomatous component of our patient's lesion might have been caused by HPV-51 infection, but involvement of HPV-51 in the development of sebaceous gland hyperplasia is unclear. There have been no previous reports of sebaceous gland hyperplasia combined with a papilloma, and this is the first case report. The association between the two lesions and their influence on each other is unknown. Squamous cell papilloma is a benign squamous epithelial tumor, originated from epithelia located in the inferior fornix, limbus, caruncle, and palpebral regions. Papilloma is one of the most common benign tumors in caruncular lesions, and a strong association exists between HPV. On the other hand, sebaceous gland hyperplasia is characterized by hyperplastic lobules with a single duct surrounded by normal cells. A family history has sometimes been reported,⁷ but no report with HPV infections. As the origin of these two tumors was different in general, it seemed to be a coincidence in the present case.

It is also unclear whether the sebaceous gland hyperplasia or the papilloma developed first. No abnormalities were observed in the other eye, and neither of these tumors was detected elsewhere. At present, there has been no recurrence after postoperative follow-up for 3 years, but we plan to continue monitoring the patient over the long term. Although the lacrimal caruncle is missing after resection of the tumor, the patient has not developed any abnormalities such as excessive lacrimation or dry eyes, and the outcome is satisfactory.

Conclusion

This might be the first report of coincidence of sebaceous gland hyperplasia and papilloma. HPV-51 was detected in the apical portion by in situ hybridization, even though the association between these two lesions was unclear.

Disclosure

The authors report no conflicts of interest in this work.

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