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Conjunctival papilloma: Clinical features, outcome, and factors related to recurrence

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Abstract:

PURPOSE: The purpose of the study was to evaluate the clinical features, treatment, and outcome of patients with conjunctival papilloma.

MATERIALS AND METHODS: Twenty-two patients (22 eyes) with biopsy-proven conjunctival papilloma between January 2005 and January 2015 in a tertiary medical center were retrospectively reviewed. Clinical profiles, treatment, outcome, and factors related to recurrence were evaluated.

RESULTS: There were 16 males (73%) and 6 females (27%), with a mean age of 47 years. The most common location of conjunctival papilloma was the caruncle (43%), followed by palpebral conjunctiva (29%), bulbar conjunctiva (14%), and fornix (14%). Recurrence developed in five patients (22.7%). The risk of postoperative recurrence was significantly related to the presence of bulbar conjunctival papilloma with corneal involvement ($P=0.043$) and surgical excision alone ($P=0.039$). One case with multiple recurrences developed nonkeratinizing carcinoma. Two young females developed conjunctival papilloma even after receiving human papillomavirus vaccinations.

CONCLUSION: The recurrence of conjunctival papilloma is not uncommon, especially for those patients underwent surgical excision alone. Surgical excision with adjunctive therapy and long-term follow-up is rational for the treatment of conjunctival papilloma.

Keywords:

Conjunctiva, human papillomavirus, papilloma, recurrence

Introduction

Conjunctival papilloma is an acquired benign epithelial tumor of the conjunctiva and may manifest as sessile or pedunculated conjunctival mass. A close causal relationship between human papillomavirus (HPV) and conjunctival papilloma has been reported.^[1] Conjunctival papilloma often requires surgical excision. Other interventions including perilesional cryotherapy, intralesional or topical interferon- α injection, carbon dioxide (CO₂) laser, topical mitomycin-C (MMC), and oral cimetidine have been reported to be as adjunctive treatments.^[2-8] Despite the

multiple choices of treatment modalities for treating conjunctival papilloma, recurrences are not uncommon. In this study, we investigate the clinical features, treatment, and postoperative outcome of conjunctival papilloma, to identify the related significant factors for recurrence.

Materials and Methods

We retrospectively reviewed the medical records of all patients with biopsy-proven conjunctival papilloma who were treated in the eye clinic of Taipei Veterans General Hospital between January 2005 and January 2015. The Institutional Review Board approved the study. The following data were obtained from patients' charts: age,

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gender, past history, tumor location, treatment, and outcome. All conjunctival papillomas were completely excised using a no-touch technique by handling only the adjacent, clinically normal tissues to avoid spreading the viral particles. Adjunctive therapies (double freeze-thaw cryotherapy, intraoperative MMC (0.3 mg/mL) application with a cellulose sponge to the involved area after surgical excision, or CO₂ laser-assisted resection) were performed in some cases. Comparison between two groups (recurrence vs. nonrecurrence) was done by Chi-square test. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS computer statistical software (version 20.0; SPSS, Chicago, IL, USA).

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the institute. Informed written consent was obtained from all patients prior to their enrollment in this study.

Results

A total of 22 eyes of 22 patients with conjunctival papilloma were included in our study, with 16 male (72.7%) and 6 female (27.3%) patients [Table 1]. The mean age at initial examination was 47.0 years (range: 14–88 years). The mean age of male patients was 52.0 ± 22.6 years and female patients was 33.5 ± 21.3 years. The age distribution shows

a peak in the age group of 21–40 years (50%) [Table 2]. Table 3 shows that the locations of conjunctival papilloma were mostly on the caruncle (43%), followed by palpebral conjunctiva (29%), fornix (14%), and bulbar conjunctiva (14%). Eight patients (36.4%) underwent surgical excision alone, and 14 patients (63.6%) received surgical excision with adjunctive therapy (cryotherapy in 8 cases, topical MMC in 3 cases, CO₂ laser and topical MMC in 1 case, and cryotherapy and topical MMC in 2 cases [Table 1]). All histopathological reports of the surgical specimens revealed typical conjunctival squamous papilloma. The polymerase chain reaction (PCR) of high-risk HPV (HPV-16, HPV-18, HPV-33, and HPV-45) was negative in all specimens (PCR for low-risk HPV was unavailable in our laboratory). Recurrent conjunctival papilloma developed in five patients (22.7%). Statistical analysis demonstrated that bulbar conjunctival papilloma with corneal involvement ($P = 0.043$) and surgical excision without adjunctive therapy ($P = 0.039$) were associated with higher recurrent rate [Table 4]. Case 6 developed recurrence from one eye to both eyes. Case 7 developed multiple recurrences (more than 10 times) after surgical excision in the past 20 years. Finally, a nonkeratinizing carcinoma developed on the caruncle and extended to lacrimal sac.

Discussion

In the current study, the incidence of conjunctival papilloma was highest among patients between 21 and

Table 1: Clinic features, treatment, and outcome of 22 patients with conjunctival papilloma

Case	Gender	Age	Location (conjunctiva)	Laterality	Treatment	Recurrence	Malignant transformation	Note
1	Female	23	Palpebral + lid margin	OS	Excision	No	No	
2	Male	57	N/A	OS	Excision	No	No	NPC
3	Male	83	Bulbar	OS	Excision	No	No	Basal cell carcinoma
4	Male	56	Fornix	OD	Excision	No	No	
5	Male	88	Bulbar + cornea	OS	Excision	Yes	No	Esophageal carcinoma Recurrence >3 times
6	Male	35	Caruncle	OD	Excision	Yes	No	Persistent recurrence
7	Male	34	Caruncle	OS	Excision	Yes	Yes	Recurrence >3 times
8	Male	68	Bulbar + cornea	OD	Excision	Yes	No	
9	Male	41	Caruncle	OD	Excision + cryotherapy	No	No	
10	Female	75	Caruncle	OD	Excision + cryotherapy	No	No	
11	Female	31	Caruncle	OD	Excision + cryotherapy	No	No	HPV vaccination
12	Male	85	Palpebral + lid margin	OD	Excision + cryotherapy	No	No	
13	Female	14	Palpebral + lid margin	OD	Excision + cryotherapy	No	No	
14	Female	29	Caruncle	OD	Excision + cryotherapy	No	No	
15	Male	35	Fornix	OS	Excision + cryotherapy	No	No	
16	Female	29	Fornix	OS	Excision + cryotherapy	Yes	No	HPV vaccination
17	Male	36	Palpebral + lid margin	OD	Excision + MMC	No	No	
18	Male	24	Palpebral + lid margin	OD	Excision + MMC	No	No	
19	Male	80	Caruncle	OD	Excision + MMC	No	No	
20	Male	52	Palpebral	OS	Excision + MMC + CO ₂ laser	No	No	
21	Male	36	Caruncle	OD	Excision + MMC + cryotherapy	No	No	
22	Male	22	Caruncle	OD	Excision + MMC + cryotherapy	No	No	

NPC=Nasopharyngeal carcinoma, HPV=Human papillomavirus, MMC=Mitomycin-C, CO₂=Carbon dioxide, N/A=Not available, OS=Left eye, OD=Right eye

40 years (50%), and there was a male predominance (72.7%). This is also the peak age at onset of genital HPV infection in sexually active adults. Our findings are consistent with those in other studies.^[9,10] The most common location of conjunctival papilloma was the bulbar conjunctiva (42%) in Ash *et al.*'s study and the palpebral conjunctiva (38%) in Sjö *et al.*'s study, respectively.^[9,11] In our study, the most common site was the caruncle (43%), which is similar to Kaliki *et al.*'s study with 23% in the caruncle.^[10] Possible factors influencing this prevalent location of conjunctival papilloma could be due to the habit of eye rubbing and tear drainage from the superotemporal fornix to the lacrimal lake, resulting in autoinoculation of HPV.^[9,10]

The recurrence rate of conjunctival papilloma has been reported to range between 3% and 27%.^[10,11] In our study, the recurrence rate is 22.7%. Especially, our study showed a higher recurrence rate (50%) in those patients treated with surgical excision alone. It is hard to identify the free margin and depth of conjunctiva papilloma during excision surgery because of conjunctival bleeding and lack of microscopic analysis. Various adjunctive therapeutic modalities such as double freeze-thaw cryotherapy, CO₂ laser, oral cimetidine, and topical MMC or interferon α -2b have been suggested to reduce the recurrence rate of conjunctiva papilloma.^[2-11] In our series, the most common treatment modality was surgical excision with adjunctive cryotherapy, and/or topical MMC, and/or CO₂ laser, which got a relatively lower recurrence rate (7%) in these patients as compared to those without adjunctive treatment (50%). The double freeze-thaw cryotherapy is a preferred method of adjunctive therapy for squamous cell papillomas with

less scarring formation and a relatively lower recurrence rate. MMC, a DNA alkylating agent, can directly disrupt rapid cell proliferation and is indicated for recalcitrant conjunctival papillomas or those refractory to prior multiple treatments. CO₂ laser-assisted resection allows for precise tissue excision with less blood loss and trauma to tissue. In the current study, two cases of conjunctival papilloma with bulbar conjunctival and corneal involvement received surgical excision alone, and both had relapse. Ocular surface reconstruction using amniotic membrane following excision of tumor, perilesional cryotherapy, and perilesional injections of interferon α -2b have been shown to be effective treatments for conjunctival papilloma with corneal/limbal involvement.^[12-14]

HPV DNA has been reported to be detected in 58%–92% of conjunctival papillomas, with HPV-6 and HPV-11 being the most common HPV type.^[1,10] In our study, there were two young females developed conjunctiva papilloma even having received prior HPV vaccinations (case 11 and 16). The FDA has approved Gardasil® (for HPV types 6, 11, 16, and 18) for use in females for the prevention of HPV-caused cervical, vulvar, vaginal, and anal cancers; precancerous cervical, vulvar, vaginal, anal lesions, and genital warts.^[15,16] However, whether HPV vaccination could provide protection against HPV-related conjunctival papilloma still requires further investigation. The PCR of high-risk HPV (HPV-16, HPV-18, HPV-33, and HPV-45) and low-risk HPV (HPV-6, HPV-11, HPV 42, HPV-43, and HPV44) were all negative in both cases. Moreover, other HPV types could also be found occasionally in the conjunctival papilloma, which is not fully protected by the HPV vaccine.

In our series, one case developed a nonkeratinizing carcinoma after multiple recurrences of conjunctival papilloma in the caruncle. Most conjunctival papillomas are benign tumors with a minimal propensity toward malignancy. Rarely, they can undergo malignant transformation, especially for those with inverted growth pattern or recurrence.^[17,18] Long-term surveillance is required for these patients.

Conclusion

Recurrences of conjunctival papilloma are not uncommon. No-touch techniques of surgical excision

Table 2: Age distribution of 22 patients with conjunctival papilloma

	Age				
	0-20 years	21-40 years	41-60 years	61-80 years	>80 years
Number of patients (%)	1 (4.6)	11 (50)	4 (18.2)	3 (13.6)	3 (13.6)

Table 3: The distribution of conjunctival sites involved in 21* conjunctival papillomas

Location	Bulbar conjunctiva	Palpebral conjunctiva	Conjunctival fornix	Caruncle
Number of patients (%)	3 (14)	6 (29)	3 (14)	9 (43)

*Case 2 was excluded because of missing data of tumor location

Table 4: Factors related to recurrence of conjunctival papilloma

	Age	Gender		Surgery		Bulbar conjunctiva and corneal involvement	
		Male (%)	Female (%)	Excision (%)	Excision + adjuvant (%)	Yes (%)	No (%)
Nonrecurrence	45.82±23.21	12 (75)	5 (83.3)	4 (50)	13 (92.9)	0	17 (85)
Recurrence	52.00±28.12	4 (25)	1 (16.7)	4 (50)	1 (7.1)	2 (100)	3 (15)
P	0.670	0.678		0.039		0.043	

with cryotherapy and/or other adjunctive therapies can prevent viral dissemination and reduce the tumor recurrence.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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