

Papilloma Development and Long-term Ciclosporin Use in Chronic Ocular Allergy With Associated Keratoconus

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Purpose: Conjunctival papillomata are squamous epithelial tumors with a strong association with human papilloma virus (HPV) types 6 and 11. They are benign conjunctival tumors that can be treated by surgical excision. We report a case where topical immunosuppressive therapy modified the local T-cell immunity in the conjunctiva resulting in papilloma development in a patient with keratoconus and a strong atopic history.

Methods: A case report of a 44-year-old man with a history of severe ocular and generalized atopy is presented. We present the problems encountered in management of his severe ocular allergy and how these impeded the management of his keratoconus.

Results: Conventional antiallergy topical medication was not producing symptom relief in this patient, and so topical immunosuppression was commenced using ciclosporin ointment 0.2%. This therapy modified the local T-cell immunity in the conjunctiva resulting in the development of papillomata which contributed to the intolerance of contact lens wear for visual rehabilitation of the keratoconus in the patient. These lesions were surgically removed but typically recurred and required further surgical excision. Adjunct cryotherapy was also performed at the time of the surgery to try to stem the recurrence of the papillomas.

Conclusions: To the best of our knowledge and following a review of the published literature using key databases that include Medline and PubMed, this is the first report confirming the development of conjunctival papillomas secondary to HPV type 6 in a ciclosporin-treated patient.

Key Words: Atopic keratoconjunctivitis—Conjunctival papilloma—HPV type 6—HPV type 11—Ciclosporin.

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Human papillomata are neoplasms of epithelial origin found in numerous anatomical locations (e.g. skin, conjunctiva, and cervix). They are characteristically lobulated with a central vascular core and may rarely undergo malignant change. Conjunctival papillomata in particular are benign squamous epithelial tumors with minimal malignant potential. A strong association exists between human papilloma virus (HPV) types 6 and 11 and the development of conjunctival papillomas.¹ We report on a case of

HPV arising on a background of ocular allergy in a patient using local long-term immunosuppressive therapy.

METHODS

A 44-year-old man with a history of atopic keratoconjunctivitis, asthma, and atopic dermatitis had been under the care of the contact lens and the external disease clinics for more than 17 years for associated keratoconus. His asthma was well controlled with the use of a regular salbutamol inhaler supplemented with the occasional use of a steroid inhaler for acute exacerbations. His atopic dermatitis was controlled with the use of topical emollients. Ocular treatment during this time comprised the use of mast cell-stabilizing agents supplemented with intermittent topical steroids for allergy exacerbations. Topical ciclosporin 0.2% ointment at night was added, both as a steroid sparing agent and to improve symptom control.

RESULTS

Seven months after commencement of ciclosporin alongside intermittent topical steroid use, bilateral large upper tarsal conjunctival papillomas were noticed (Fig. 1). These lesions started interfering with his contact lens wear for his keratoconus and necessitated their surgical removal. After surgery, ciclosporin ointment use continued twice daily to control symptoms along with topical mast cell-stabilizing agents only. Papilloma recurrence was observed within 12 months and further excision was necessary

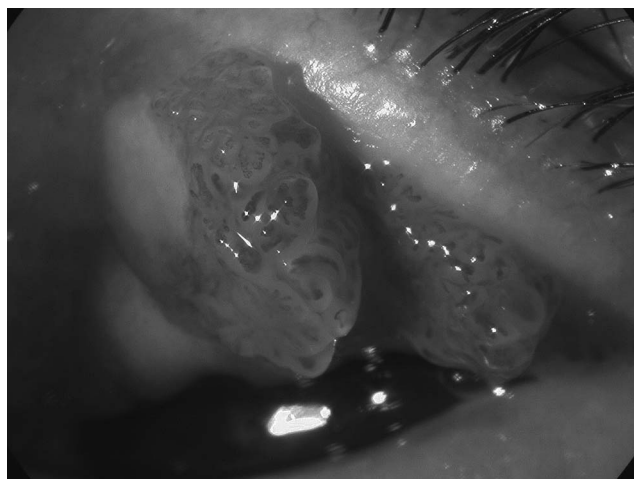


FIG. 1. Papillomatous lesions on the upper tarsal conjunctiva.

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TABLE 1. Laboratory Analysis for HPV in the Sample From the Patient

HPV6	Absorbance Value
Hybridization positive control	43,378
Hybridization negative control	409
Cut-off value	1243
Patient sample	63,991

HPV, human papilloma virus.

3 years after the first procedure. Over the course of the next 12 months, his conjunctival papillomas again recurred. Histopathology of the excised tissue confirmed squamous papilloma, and the analysis of the excised lesion by direct polymerase chain reaction followed by an enzyme-linked immunosorbent assay for the positive samples confirmed the presence HPV type 6 DNA (Fig. 2 and Table 1). Adjunct treatment with cryotherapy was applied at the time of the second and third surgical resections of the papillomas. Of note, papillomatous lesions were not present in any other part of the patient's body.

DISCUSSION

Conjunctival papillomas are most common among people aged 20 to 39 years, and there is a male preponderance.² They are benign conjunctival tumors that can be treated by surgical excision. Recurrent lesions are common and tend to grow more rapidly.³ The exact etiology of these lesions has not been established, but it is known that HPV is a causative factor. Human papilloma virus is an oncogenic double-stranded DNA papovavirus that infects keratinocytes and causes benign and malignant squamous epithelial tumors. Over 100 subtypes have been identified, but low-risk types 6 and 11 and high-risk types 16 and 33 are most commonly found in conjunctival papillomas.¹ Conjunctival HPV infection may be established during delivery through an infected birth canal, by sexual contact, or by autoinoculation. However, HPV may be present, albeit rarely, in normal oral and nasal mucosa.⁴ Immunosuppressed organ-transplant recipients suffer particularly high incidences of HPV infection that

are directly associated with the extent and duration of their immune suppression, and an association between HIV and an increase in the incidence of conjunctival carcinoma has also been found.⁵ The immunodeficiency secondary to HIV or local immunosuppression may facilitate the oncogenic effects of HPV by altering the local host susceptibility to HPV infection and impairing immune tumor cell surveillance.

To the best of our knowledge and following a review of the published literature using key databases that include Medline and PubMed, this is the first report confirming the development of conjunctival papillomas secondary to HPV type 6 in a ciclosporin-treated patient. Ciclosporin was used as a local immunosuppressant in this patient, and it is postulated that this immunosuppressive therapy lead to the reactivation of the virus in this patient. Ciclosporin is believed to bind to the cytosolic protein cyclophilin (immunophilin) found in T-lymphocytes.⁶ This complex of ciclosporin and cyclophilin inhibits calcineurin, an enzyme which under normal circumstances is responsible for activating the transcription of interleukin-2 and the resulting T-cell clonal expansion. It also inhibits lymphokine production and interleukin release, and therefore leads to a reduced function of effector T-cells. Modification of local T-cell immunity in the conjunctiva may therefore facilitate the development of conjunctival papillomata in patients who have HPV exposure. Human papilloma virus encodes the E6 and E7 oncoproteins that act on the tumor suppressor genes *p53* and *Rb*, respectively,^{7,8} and increases transforming growth factor beta (TGF- β) promoter activity. TGF- β controls proliferation, differentiation, and other functions in most cell types. Compared with the high risk HPV types 16 and 18, which may be most frequently associated with conjunctival intraepithelial neoplasm, the HPV type 6 E6 and E7 oncoproteins are seemingly less effective at transforming epithelial cells in vitro; therefore, their correlation with benign conjunctival papilloma.⁹

A high incidence of HPV has been previously reported in ciclosporin-induced gingival overgrowth in renal transplant recipients.¹⁰ Seibel et al.¹¹ demonstrated the development of similar lesions in dogs treated with ciclosporin. All dogs developed papillomatous hyperplasia by the seventh week of treatment with regression of the lesions occurring spontaneously after termination of ciclosporin administration. Multiple papillomatous lesions (facial and systemic) have also been described in patients treated with long-term ciclosporin after transplantation¹² or for control of atopic dermatitis.¹³ Although the exact mechanism of the action of ciclosporin in papilloma production secondary to HPV remains unclear, the finding in this case report is in concordance with the findings of the study by Seibel.

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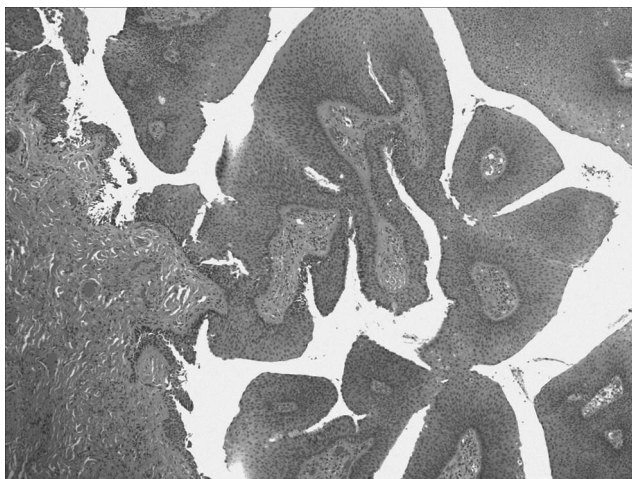


FIG. 2. A papillomatous proliferation of nonkeratinising stratified squamous epithelium overlying a fibrovascular core. No significant nuclear pleomorphism or mitotic activity was obvious in the papillomatous lesions (Hematoxylin-eosin stain; $\times 40$).

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