

## Case Report

# Cancerous Tonsillar Hypertrophy caused by Human Papilloma Virus

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### ABSTRACT

Human papillomavirus (HPV) is associated with the development of most anogenital carcinomas, including cervical cancer and has more recently been suggested to be a risk factor for a subset of head and neck squamous cell carcinoma. The prevalence of HPV in normal oral mucosa ranges from 0.6% to 81%. A 15-year-old female presented with complaints of chronically progressive pain on swallowing since 3 years. Examination revealed bilateral Grade III tonsillar enlargement with multiple warty appearances over the surface of the tonsils. Subsequently, she underwent tonsillectomy, and histopathologic study revealed tonsillar crypts lined by stratified squamous epithelium with focal koilocytic changes. PCR study detected HPV 11 DNA. The presence of HPV in the oral cavity and upper respiratory tract mucosa is of great importance since several studies have demonstrated an association of HPV with a great variety of benign and malignant lesions. The easy access to the tonsillar crypts and the favorable microenvironmental factors of the crypts may be causes of the high prevalence of HPV in nongenital regions. A rare case of benign papillomatosis of the tonsil is presented. The need for a long-term follow-up is highlighted to study the possibility and risk factors for malignant transformation.

**KEYWORDS:** *Chronic tonsillitis, human papillomavirus, tonsillectomy*

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## INTRODUCTION

Human papillomavirus (HPV) is associated with the development of most anogenital carcinomas, including cervical cancer and has more recently been suggested to be a risk factor for a subset of head and neck squamous cell carcinoma.<sup>[1]</sup> Even though HPV is well known to be related to several diseases with significant morbidity and mortality, few researchers have attempted to determine the frequency that HPV colonizes the tonsils.<sup>[2]</sup> The prevalence of HPV in normal oral mucosa ranges from 0.6% to 81%.<sup>[3]</sup>

Human papillomavirus may be postulated to play a role in the pathogenesis of palatine tonsillar cancer, not only due to its morphological similarities to cervical cancer but also because the mucosal squamous epithelium, similar to that of the uterine cervix, is easily exposed to viral infection.<sup>[3]</sup> HPV infection is prevalent in the oropharyngeal mucosal regions, and the tonsil is the most commonly affected anatomical region in the oropharynx, but the presence of HPV infection associated with benign lesions of the tonsils are a relatively rare phenomenon.

## CASE REPORT

A 15-year-old female presented to the outpatient department of Otorhinolaryngology and Head and Neck surgery of a tertiary care center in South India with complaints of chronically progressive pain on swallowing recurrent intermittent sore throat, and mild difficulty in swallowing which was slowly progressive since 3 years. The patient gave no history of change in voice, difficulty in breathing, snoring, mouth breathing, or painful neck swelling. The patient had been prescribed several courses of antibiotics and analgesics by various local general practitioners over the course of this 3-year period.

General examination was unremarkable. On local examination, she had bilateral Grade III tonsillar enlargement with multiple warty appearances over the

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surface of the tonsils [Figure 1]. She also had bilateral nontender jugulodigastric nodes. Subsequently, she underwent tonsillectomy, and the specimen [Figure 2] was sent for histopathologic examination and polymerase chain reaction (PCR) study as well. The histopathologic study revealed tonsillar crypts lined by stratified squamous epithelium with focal koilocytic changes [Figure 3]. PCR study detected HPV 11 DNA.

DNA was extracted from specimen, the concentration and purity were confirmed with spectrophotometry using the wavelength ratio of 260/280 nm. Specimens were tested for the presence of HPV using improved PGMY 09/11 L1 consensus primer systems, which amplify a 450-bp fragment of the L1 open reading frame of a broad spectrum of HPV genotypes. PCR products were analyzed by 2% ethidium bromide-stained agarose gel electrophoresis. Thereafter, PCR products positive for HPV were typed using the Roche HPV Consensus PCR/Line Blot Genotyping reagents. The patient was given prophylactic HPV vaccination during follow-up. The patient was asymptomatic at 1 year follow-up, and examination did not reveal any recurrences in the tonsillar fossa.

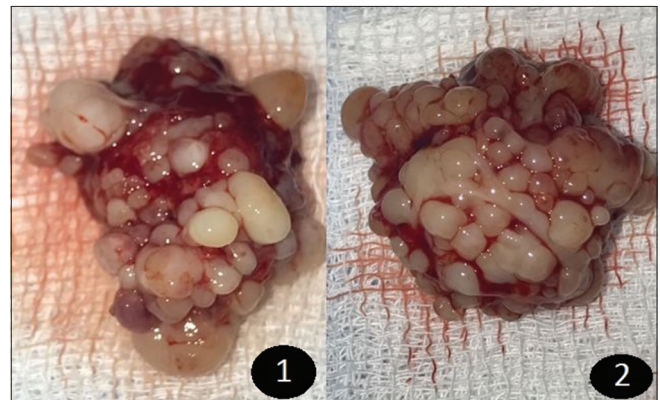
## DISCUSSION

The HPV virion is a double-stranded, circular DNA genome comprised of eight open reading frames with early (E) and late (L) genes. The L1 gene encodes for the major capsid protein and is well preserved across numerous genotypes. All known HPV types are exclusively epitheliotropic and depend on epithelial differentiation for completion of their life cycle. Infection and virus uncoating begins in the basal layer where expression of early (E) genes occurs, which maintains the viral genome and retards terminal differentiation of basal cells stimulating cell-cycle progression. In the mid or upper epithelial layers, expression of late (L) genes occurs allowing amplification and packaging of virions into infectious particles. When infection by a virus occurs, the cell-mediated arm of the immune system is activated leading to the production of IL-2 that serves as a critical messenger in the stimulation of helper and cytotoxic T cells.<sup>[4,5]</sup>

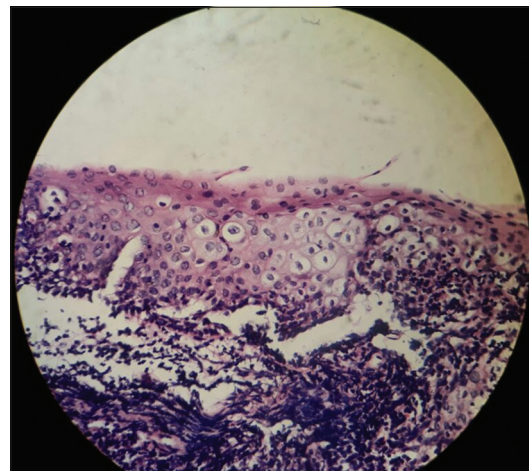
It is known that smoking, starting a sexual activity and giving birth at an early age, having numerous sexual partners, and using oral contraceptives correlate with a higher risk for HPV infection in women.<sup>[6]</sup> Several nonsexual modes of transmission can be proposed for pediatric HPV infections, including vertical transmission, horizontal transmission, and autoinoculation. Vertical transmission is divided into 3 subtypes: periconceptual (time around fertilization), prenatal (during pregnancy), and perinatal (during birth and immediately



**Figure 1:** Examination of oropharynx revealing bilateral Grade III tonsillar enlargement with multiple warty appearances over the surface of the tonsils



**Figure 2:** Posttonsillectomy specimens showing multiple warty appearances over the surface of the tonsils



**Figure 3:** Section from crypt showing stratified squamous epithelium with koilocytic change (H and E, x40)

thereafter) transmissions. HPV transmission could also be the result of close contacts of the fetus with infected cervical and vaginal cells of the mother during delivery. In horizontal transmission, children might acquire HPV

infection from breast milk during breastfeeding, from householders, and from friends through kissing and digital contacts. Although the consequences of vertical and horizontal transmission in early childhood HPV infection are still unknown, HPV infection may induce HPV-specific humoral tolerance. In this case, prophylactic HPV vaccines should be administered at birth.<sup>[7]</sup>

The exact mechanism of HPV infection in nongenital regions remains uncertain, but the easy access to the tonsillar crypts and the favorable microenvironmental factors of the crypts may be causes of the high prevalence of HPV in nongenital regions. HPV DNA is detected predominantly in the epithelium lining the tonsillar crypt by *in situ* hybridization.<sup>[8]</sup>

The presence of HPV in the oral cavity and upper respiratory tract mucosa is of great importance since several studies have demonstrated an association of HPV with a great variety of benign and malignant lesions. Some of the most frequent benign lesions of the oral mucosa related to HPV are oral papilloma, focal epithelial hyperplasia, and leukoplakias. The frequency of HPV in head and neck cancer patients varies between 8% and 50%; it is believed that its detection may be dependent on several factors including the molecular technique utilized (Southern blot hybridization, PCR, *in situ* hybridization), the treatment of the sample material (fresh, frozen, paraffin embedded), ethnic and geographical differences, and the anatomic site of the lesion.<sup>[9]</sup>

HPV DNA can be detected in tissue specimens by various methods, including *in situ* hybridization, HPV DNA assays, and HPV nucleic acid detection with target amplification. As a result of its increased sensitivity, PCR has become a popular method for molecular diagnosis of HPV infection. Furthermore, PCR for HPV DNA can be designed to amplify a single HPV genotype or a broad spectrum of HPV types based on the primers used. Type-specific PCR is labor-intensive and expensive leaving broad-spectrum amplification better suited for molecular screening of HPV infection.<sup>[10]</sup>

The detection of HPV DNA in tumor-free tonsils has been reported in only a few studies, and others failed to detect the viral DNA in tonsillitis samples. The overall frequency of HPV DNA in the normal tonsillar mucosa or benign tonsillar lesions is 8.5%, consisting of 70% with HPV-16 and 30% with HPV-6/11. HPV DNA is seldom detectable in normal tonsillar exfoliated cells, suggesting that HPV DNA either locates in the crypt epithelial cells or normal tonsils do not harbor HPV DNA.<sup>[11]</sup>

## CONCLUSION

Benign papillomatosis of the tonsils is rare and further studies with a long-term follow-up are warranted to clarify whether or not this condition is related to the development of HPV-related cancer. The appropriate modality of treatment of this condition also needs to be developed, although in our case surgery was effective and long-term follow-up has not revealed a recurrence.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patients understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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