Original Article

A set of thoughts on a series of patients with oral viral papillomas caused by the HPV 6 and 11 viruses: A brief review

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Abstract

Introduction: Papillomas are associated with human papillomaviruses (HPV) and are commonly benign. Typically, the clinical presentation establishes the diagnosis, and treatment comprises excision and histological analysis.

Objective: In light of our series of 39 patients with viral papillomas of the oral mucosa, we would like to express our concerns regarding the treatment of patients diagnosed with HPV 6 and 11-positive oral papillomas.

Materials and Methods: The research is based on an analysis of 39 patients with oral papillomas who underwent conventional HPV viral testing. The analysis was conducted utilizing the in situ hybridization method. Patients tested positive for HPV subtypes 2, 4, 6, 11, 16, 18, 31, 33, and 51. More than fifty percent of individuals tested positive for HPV 6 and 11.

Conclusion: HPV subtypes have been identified in lesions with comparable clinical presentation. Many of our patients carry the HPV subtypes 6 and 11, which have been associated to sexual transmission. However, more transmission routes are also possible. The ideal treatment for us would be a referral to a Venereologist for a thorough sexually transmitted illness examination.

Keywords: HPV 6, HPV 11, oral viral papilloma

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INTRODUCTION

Numerous oral lesions have been linked to the human papilloma virus (HPV). These are mainly benign exophytic proliferation of the oral epithelium produced by various HPV genotypes. Subtypes 6 and 11, which have a low chance of developing cancer, are the most prevalent and produce condyloma acuminatum in both the oral cavity and anogenital area.[1] Additionally, HPV 6 and 11 have been detected in oral squamous papillomas.[2] Because all HPV-related oral lesions exhibit clinical characteristics, a biopsy is required for a correct diagnosis. In histopathologic sections, koilocytes can be seen.[1]

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Observing many patients with oral mucosal viral papillomas sparked our concerns regarding the treatment of patients with HPV 6 and HPV 11-positive oral papillomas.

It is well-established that papillomas are completely benign.[2] Clinical diagnosis is utilized frequently in medical practice [Figure 1 shows typical cases]. The treatment consists of surgical removal followed by a histological examination.[2]

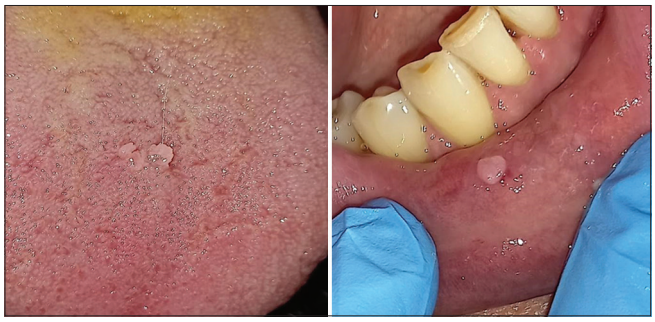

Figure 1: Squamous papilloma on the tongue (HPV 6 positive) and the lip (HPV 2 positive), small pedunculated lesions with short spiky projections

Based on our prior knowledge, a histological examination of the koilocytes for the presence of HPV viruses is advised [see Table 1].

RESULTS OF OUR CASE SERIES

Over the course of the preceding five years, we discovered 39 cases of oral viral papillomas in our own patient population [Table 1]. The average age of the patients was 40, ranging from 20 to 80 years old. The majority of the patients were male (61%, 24/39).

As part of our routine, we send all samples for histology and HPV detection.

Table 1: Patients' features

Gender	Age	Site	Histology	Hpv Type Detected With Ish
Male	35	Buccal mucosa (R)	Oral squamous papilloma with mild focal epithelial hyperplasia	2
Male	80	Hard palate	Oral squamous papilloma with mild focal epithelial hyperplasia	2
Male	33	Labial commisure of the mouth (R)	Oral squamous papilloma with mild focal epithelial hyperplasia	2
Male	33	Ventral surface of tongue	Oral squamous papilloma	2
Male	31	Buccal mucosa	Oral squamous papilloma	2
Female	52	Lower lip mucosa (L)	Oral squamous papilloma	2
Female	63	Border soft-hard palate	Oral squamous papilloma with mild focal epithelial hyperplasia	2
Female	58	Tongue	Oral squamous papilloma with mild focal epithelial hyperplasia	2
Female	57	Buccal mucosa (R)	Oral squamous papilloma	2
Female	27	Tongue and soft palate	Oral squamous papilloma	2
Female	52	Lower lip mucosa	Oral squamous papilloma with mild focal epithelial hyperplasia	4
Male	45	Tongue (R)	Oral squamous papilloma	6,11
Male	22	Floor of mouth on submandibular salivary Gland's duct	Oral squamous papilloma	6,11
Male	30	Lower lip mucosa (R)	Oral papilloma	6,11
Male	32	Mandibular gingiva (R)	Oral squamous papilloma	6,11
Male	49	Labial commisure of the mouth (R)	Oral papilloma	6,11
Male	22	Buccal mucosa (L)	Oral squamous papilloma	6,11
Male	39	Lateral border of tongue (R)	Oral squamous papilloma	6,11
Male	50	Tip of tongue	Oral squamous papilloma	6,11
Male	28	Lateral border of tongue (L)	Oral squamous papilloma	6,11
Male		Buccal mucosa (L)	Oral squamous papilloma	6,11
Male	38	Ventral surface of tongue	Oral squamous papilloma	6,11
Male	53	Hard palate	Oral squamous papilloma	6,11
Male	40	Soft palate	Oral squamous papilloma	6,11
Male	22	Buccal mucosa (L)	Oral squamous papilloma	6,11
Female	29	Ventral surface of tongue (R)	Oral squamous papilloma	6,11
Female	27	Ventral surface of tongue (L)	Oral squamous papilloma	6,11
Female	26	Tongue	Oral suqamous papilloma	6,11
Female	40	Buccal mucosa (R)	Oral squamous papilloma	6,11
Female	51	Dorsal surface of tongue	Oral squamous papilloma	6,11,16,18,31, 33,51
Female	28	Hard palate	Oral squamous papilloma	6,11,16,18,31,33
Female	47	Buccal mucosa (L)	Oral squamous papilloma with mild focal epithelial hyperplasia	6,11,31,33
Female	27	Tongue and soft palate (2 lesions)	Oral squamous papilloma without epithelial hyperplasia	2
Male	50	Palate and lips (3 lesions)	Oral squamous viral papilloma with mild focal epithelial hyperkeratosis	2
Female	27	retromolar area	Oral squamous viral papilloma with mild focal epithelial hyperkeratosis	2
Male	38	Tongue (3 lesions)	Oral squamous viral papilloma with mild focal epithelial hyperkeratosis and mild epithelial dysplasia	6,11
Male	54	Tongue lateral left border	Oral squamous viral papilloma without epithelial dysplasia	4
Male	47	Soft palate	Oral squamous viral papilloma without epithelial dysplasia	2
Male	45	Soft palate	Oral squamous viral papilloma without epithelial dysplasia	2

The standard *in situ* hybridization process is used by the laboratory to detect the following:

Low-Risk HPV Subtypes:

6, 11, 40, 42, 43, 44, 55, 61, 70, 72, 81, 83, 84, 89.

High-Risk Subtypes of the HPV Virus:

16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, 82, 85.

Patient samples had HPV 2, 4, 6, 11, 16, 18, 31, 33, 51 copies.

Each patient was advised that they had a benign condition and dismissed with instructions to return if the disease recurred. More than 50% (21/39) were positive for HPV 6 or 11. Three of the patients who tested positive for HPV 6 and 11 also tested positive for other subtypes (16, 18, 31, 33, 51). All three were females who were advised to consult a gynaecologist.

DISCUSSION

Papillomas, warts and condylomas are all common skin lesions that can manifest on the oral mucosa. It is difficult to make clinical and histologic distinctions.[2] Papillomas are easily identified as oral lesions with a papillary surface that are isolated. Some authors suggest that certain HPV subtypes are predisposed to one or more types of lesions, but this is mainly inconclusive.[2] To be certain of the viral association, we treat all papillary oral lesions as 'viral papillomas' and identify their HPV subtypes. Multiple papillary lesions may be caused by inherited conditions; Heck's disease, also known as focal epithelial hyperplasia, is a rare proliferation of the oral mucosa that primarily affects native populations of Central and South America. The vast majority of cases are caused by types 13 or 32 of HPV.[3] Multiple hamartoma syndrome, also known as Cowden syndrome (CS), is another condition to consider, especially if the gingiva has multiple papillary-like lesions. This is a rare case of autosomal dominant genodermatosis characterized by variable penetrance and incomplete expressivity. CS mutations are caused by PTEN gene mutations. Multiple lesions resembling oral papillomas could be an indication of CS.[4]

HPV 6 and 11 were found in a high proportion of our patients (22 of 39 tested positive). Others have used PCR to identify HPV 6 and 11 positive oral squamous papillomas,[5] which is effective. *In situ* hybridization detects nucleotide sequences in cells, tissue sections and whole tissue. This method uses a nucleotide probe to bind to a DNA or RNA target sequence. Radio-, fluorescent- or antigen-labelled bases can label these probes. Autoradiography, fluorescence microscopy or immunohistochemistry are used depending on the probe. *In situ* hybridization is used in research and clinical diagnostics.[6] Because our laboratory's *in situ* hybridization technique has been standardized, the cost per case (including histological inspection) is 40% less than for PCR (histological examination included). As a result, the method can be used to supplement standard histology examinations at a low cost.

Our sample size is insufficient for concluding gender predilection and the location of viral oral papillomas. In our study, men outnumbered women, and lesions were detected in all regions of the oral mucosa, including the tongue, lips, palate and gingiva [Table 1].

Several subtypes of HPV were detected in our patients [Table 1]. The Gardasil and Garsasil 9 vaccines protect against many of the HPV subtypes we found, which are thought to be sexually transmitted.[7] Because our patients are on average 40 years old, it is possible that the vaccine was not available to them when they were in their teens (when the vaccine is commonly administered). Possibly, in the next few years, the effects of the vaccine will alter the frequency of oral viral papillomas and the HPV subtypes detected in them. HPV 6 and 11 subtypes were the most difficult for us to communicate about the transmission and relevance to sexual behaviour and the connection between HPV subtypes and cancers and sexual transmission. A lack of high-quality evidence-based data as well as misinformation on HPV infection on the internet were challenges we had to overcome.

Sexual contact is one route for the spread of HPV 6 and 11.[2] However, non-sexual forms of transmission, such as hand-to-mouth transmission and vertical transfer during pregnancy or labour, should be addressed.[8] Data indicate that HPV 6 and 11 are also widespread.[2] Upper aerodigestive tract papillomas also harbour HPV 6 and 11 and have a low risk of cancer.[9]

Due to the fact that sexual transmission is not the only mode of transmission and the stress that referring a patient to a specialist in sexually transmitted diseases may cause, we typically refrain from referring every patient for further evaluation by a specialist in venereal diseases. But is this acceptable? Eighty per cent of sexually active women will contract HPV at some point in their lives, according to estimates. Chronic genital infection with high-risk HPV is associated with virtually all cervical cancers and precancerous

lesions. Growing evidence has linked HPV infections to the development of head and neck malignancies, especially oropharyngeal carcinoma. Up to 4.5 per cent of all new cases of cancer worldwide and 8 per cent of all new cases of cancer in women are caused by HPV infections.[10] All of this information is readily accessible to every patient via the internet. How will we respond to patients' genuine question: 'Does the presence of a possible sexually transmitted virus in a mouth lesion indicate that we have a sexually transmitted disease?' Am I at risk for cancer?

As a result of this discourse, several ideas surfaced. Would it be appropriate for the oral medicine specialist to provide a lucid response? Despite the presence of viruses 6 and 11 in lesions with a typical oral squamous papilloma histological appearance, we cannot definitively answer this question due to the lack of relevant data.

Consequently, how should we approach the prospect of future sexual transmission? We like to underline that these individuals cannot receive medically essential therapy at the dental-oral medicine clinic.

Regarding sexually transmitted infections, we believe that referral to a skilled physician is the most effective treatment option, and dermatologists are, by definition, venereologists. Lesions such as condylomata (condylomas) appearing in the genitals at the same time as HPV 6 and 11 oral infection could indicate sexual transmission.

We believe that informing patients about the presence of HPV 6 and 11 in oral lesions is an essential component of their care. After evaluating our education and expertise as oral medicine specialists, analysing a large number of patients with oral papillomas who tested positive for HPV 6 and 11 and taking into account the vast and diverse information available to anyone on the internet, we determined that we should begin referring all patients who tested positive for HPV 6 and 11 to dermatologists. To adhere to the Hippocratic precept of 'first, do no damage', we feel that they must be sent to a dermatologist-venereologist for a clinical evaluation and information on sexually transmitted diseases. The objective here is not to avoid awkward questions, but rather to take a rational medical stance about sexually transmitted diseases; this is the most crucial factor. A dermatologist-venereologist has the skills and ability to inspect the vaginal and perinatal regions, as well as the knowledge and experience to educate patients effectively.

In addition, because the quadrivalent vaccine (Gardasil®, which protects against HPV types 6-11-16-18) is regarded as highly effective at preventing HPV 6 and 11 infections,[11] we must record whether patients are vaccinated and, if male, whether they are aware of the vaccination status of their current or previous partners. This would help us determine the efficacy of the vaccination in the Greek population. A US population study found that HPV vaccination was associated with a decreased prevalence of vaccine-type oral HPV among young persons in the US. Due to low vaccination rates, the effect on the population as a whole was negligible, and especially so for males.[12]

The purpose of this article is to share our experiences and thoughts on a seldom-discussed topic. We suspect that other doctors may have the same concerns. Therefore, this is a productive dialogue.

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Conflicts of interest

There are no conflicts of interest.

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