

Possible Role Of Human Papilloma Virus In Oral Diseases- An Update

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Abstract

Human papillomaviruses (HPV) has been an area of interest since last two decades because of its potential role in the pathogenesis of malignant tumors. Approximately 35 years ago a role of human papillomaviruses (HPV) in cervical cancer has been postulated. Today it is well established that this very heterogeneous virus family harbours important human carcinogens, causing not only the vast majority of cervical, but also a substantial proportion of other anogenital and head and neck cancers. This review will cover some of the pathogenetic aspects of papillomavirus research; it tries briefly to analyze the present state of linking HPV to human cancers and other oral lesions and will discuss some emerging developments.

INTRODUCTION

HPV infection is known to be a necessary element for the development of cervical cancer in women, and is also a risk factor for the development of anal, penile, and vulvar cancers.¹ Recently HPV infections in oral cavity have also been proposed. The oral cavity is lined by a mucous membrane consisting of a stratified squamous epithelium and lamina propria made up of dense connective tissue. The squamous epithelium of the gingiva, hard palate and the dorsum of the tongue is completely keratinized with a superficial horny layer, whereas in the lip, cheek, vestibular fornix, alveolar mucosa, floor of mouth and soft palate, the epithelium is non-keratinized. Thus, the histology of oral mucosa resembles that of the uterine cervix, other lower genital tract or skin, depending on the anatomic site. On the basis of these morphological similarities, one can anticipate the presence of both the mucosal and cutaneous human papilloma virus (HPV) types in different squamous cell lesions of the oral mucosa.² Such benign oral lesions include squamous cell papilloma (SCP), condyloma, verruca and focal epithelial hyperplasia (FEH), leukoplakia, lichen planus, oral squamous cell carcinoma shown to be linked with HPV. The role of HPV in premalignant and malignant oral lesions has been a controversial issue. However, a recent meta-analysis has confirmed HPV as an independent risk factor for oral carcinoma. HPV is the most prevalent infection world wide with several new cases diagnosed every year.²

HPV GENOME AND ITS IMPLICATION IN ONCOGENIC MECHANISM

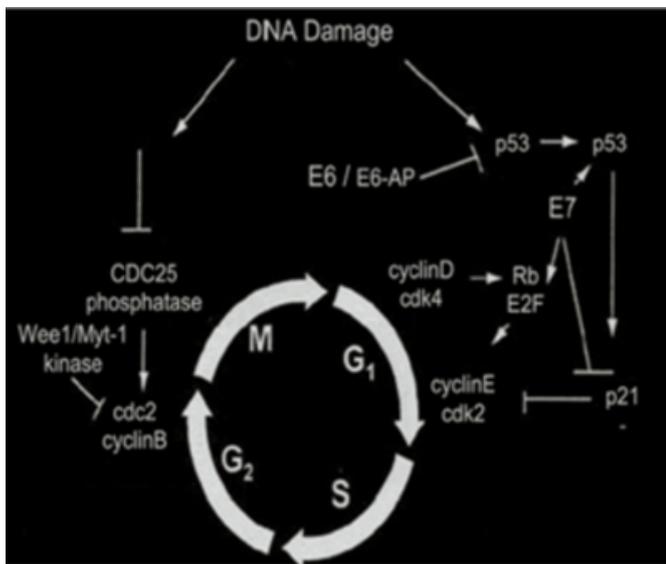
Human papilloma virus (HPV) Papilloma viruses are epitheliotropic viruses present in the skin and mucosa of several animals. In humans, more than 70 types have been described.³ Mucosal and genital HPVs, consisting of about 30 types, are divided into low risk (HPVs 6, 11, 42, 43 and 44) and high risk (HPVs 16, 18, 31, 33, 35, 45, 51, 52 and 56), according to their presence in malignant lesions of the cervix.⁴ Recognized initially as sexually transmitted agents, HPVs are now considered human carcinogens.⁵ Functionally high risk HPV infection contributes to carcinogenesis and tumor progression predominantly through the actions of two viral oncogenes, E6 and E7. These oncogenes are consistently expressed in cervical cell lines and in human cancers.^{6,7} Both of these oncogenes interact with and inhibit the activities of critical components of cell cycle regulatory systems, in particular E6 with p53 and E7 with Rb.^{8,6,7} The E7 protein interacts with pRB and inactivates this cellular protein.⁹ As a consequence, E2F transcription factor is released from pRB-E2F complex, leading to transcriptional activation of several genes involved in cell proliferation.¹⁰ Binding of the E6 protein to the p53 promotes the degradation of the latter through a ubiquitin-dependant proteolysis system. Also of significance is that on completion of the degradation of p53 by the ubiquitin-dependant proteolysis system, the E6 protein is free to interact again with remaining p53 molecules, leading to further degradation of the latter.¹¹ The products of genes E6

and E7 are essential in the process of HPV induced cellular immortalization and transformation.^{12,13} The variants are thought to differ in their biological properties and in their contribution to carcinogenesis.

The different type of viruses are characterised by genotypic variations in DNA base sequences of E6 and E7. it is this genotypic variation that permit stratification of virus oncogenic phenotype into high, intermediate and low risk types. Eg. E7 protein of HPV 16 is more oncogenic than E7 protein of HPV 6.¹⁴

Figure 1

Figure 1: A model explaining the interaction of HPV E6 and E7 with tumour suppressor genes functioning in cell cycle.



DIAGNOSTIC METHODS TO DETECT HPV INFECTION

Until recently, diagnostic laboratory testing for HPV was impossible since the virus does not grow in tissue cultures or in laboratory animals. Currently, with recent technologic advancements in molecular biology techniques for HPV testing, scientists have isolated more than 120 different HPV types.^{15,16,17,18}

- Light microscopy
- Electron microscopy
- Non amplified techniques:
 - DNA in situ hybridisation
 - Southern and dot blot hybridisation
- Molecular methods:

- Target amplification e.g PCR
- Probe amplification
- Signal amplification

ORAL MANIFESTATION OF HPV INFECTION SQUAMOUS CELL PAPILOMAS

SCP is a relatively common benign tumor of the oral epithelium.¹⁹ Frithiof and Wersa demonstrated viral particles closely resembling HPV in oral papillomas already in 1967.²⁰ Jenson et al. were the first to report, in 1982, that 2/5 oral SCPs expressed HPV common structural antigens.²¹ In the world literature by early 1998, the overall detection rate for HPV DNA was 49.8% of the analyzed 223 papillomas.²² The most prevalent HPV type was HPV 6, followed by HPV 11. HPV 16 has also been detected in some oral papillomas.

Focal epithelial hyperplasia (FEH), or Heck’s disease, was first described in detail by Archard et al.²³ although earlier reports had been published.²⁴ FEH presents clinically as multiple, isolated, pink, domeshaped nodules separated by normal oral mucosa.²⁵ The histologic appearance is diagnostic for FEH with epithelial hyperplasia of varying degree resulting in elongation and occasional anastomosis of the rete ridges (‘bronze age battle - axe’ appearance), hyperchromatism and enlargement of nuclei, and degeneration of epithelial cells.^{23,26} The degenerating epithelial cells resemble cells in various phases of mitosis (‘mitosoid’ cells).²⁶ Papilloma virus (1,6,16,32) have been repeatedly observed in FEH suggesting its viral etiology. Beaudenon et al. described a new HPV type, HPV 32 in FEH. Since then, several papers have provided more data on the association of FEH with HPV type 32, and have shown that HPV types 13 and 32 are detected in 75–100% of the FEH cases.²⁷ Overall, 147 FEH lesions have been analyzed for the presence of HPV DNA, with the detection rate of 80.3% (118/147).²⁸

CONDYLOMA ACUMINATUM

Condylooma acuminatum (venereal wart) is generally regarded as an sexually transmitted disease affecting the skin and mucous membranes of the anogenital tract.²⁹ Currently, it is accepted that oral condyloomas can arise not only by oral sex but also by autoinoculation or as a result of maternal transmission. The first report on the presence of HPV particles in an oral condylooma lesion reported as an abstract in 1976 and published as a case report in 1980 by Gysland et al.³⁰ Wysocki and Hardie first detected HPV DNA in an oral

verruca lesion using electron microscopy.³¹ As early as 1982, Lutzner et al. reported the presence of HPV type 2a in one verruca by Southern blot hybridization.³² Subsequently, immunohistochemistry was used to verify the expression of HPV antigens in oral warts, and HPV detection rates from 45% to 100% have been reported. Oral condyloma is associated most often with the low-risk HPV types 6 and 11, and less commonly with the high-risk types 16, 18, 31, 33, and 35.^{33,34,35,36,37}

VERRUCA VULGARIS (ORAL WARTS)

Verruca vulgaris or common wart is the most prevalent HPV lesion of the skin, but is also found in oral mucosa. They appear as firm, whitish, sessile circumscribed exophytic lesion showing epithelial hyperkeratinisation with elongation of rete ridges. Wysocki and Hardie first detected HPV DNA in an oral verruca lesion using electron microscopy.³¹ As early as 1982, Lutzner et al. reported the presence of HPV type 2a in one verruca by Southern blot hybridization.³² Subsequently, immunohistochemistry was used to verify the expression of HPV antigens in oral warts, and HPV detection rates from 45% to 100% have been reported. The most common HPV2 found in oral warts is HPV followed by HPV 57.^{33,34,35,36}

ORAL LICHEN PLANUS

Lichen planus (LP) is a chronic inflammatory mucocutaneous disorder. Although first described almost 150 years ago, and more than 5200 papers were present in the database PubMed in January 2007, many aspects of the pathogenesis of LP are yet not fully understood. Immunologic factors, medical problems like hypertension and diabetes have been considered as possible causes. Recently viral etiology of it has also been proposed, Maitland et al reported 87% (7/8) of OLP biopsies containing HPV DNA.³⁸ Kashima et al have demonstrated four out of 22 OLP specimens being positive for HPV structural proteins.³⁹

VERRUCOUS CARCINOMA

In 1948, Ackerman first used the term verrucous carcinoma to describe a variant of SCC found in the oral cavity. Since then this lesion, also known as Ackerman's tumor, has been recognized as a locally invasive, nonmetastasizing SCC with a characteristic gross and microscopic appearance, occurring in several locations of the oral cavity, lips and larynx as well as in the genital tract.^{40,41,42} Etiopathogenesis of it is unclear but studies has shown strong association with inhaled or smokeless tobacco or/and viral activity associated with HPV.

Recent studies have confirmed the association between HPV and verrucous carcinoma by detecting HPV by restriction fragment length polymorphism, PCR, DNA in situ hybridization.⁴³ Interestingly, the most prevalent HPV type was HPV 6/11 (47%), followed by HPV 16/18 (35.3%) and HPV 2 (17.7%). This is also in alignment with the frequent discovery of HPV 6 or 11 in genital verrucous carcinomas.⁴⁴

ORAL LEUKOPLAKIA

Leukoplakia is a precancerous lesion characterised by white patch which histologically shows the varying degree of dysplasia including in situ and early carcinoma. It is suggested to be strongly associated with smokeless and smoking tobacco.⁴⁵ According to many reports, HPV 16 related virus has been found in more than 80% of oral leukoplakias, irrespective of degree of dysplasia.³⁸ According to sand et al 31% of lesions were positive for HPV 16 and 6/11.⁴⁶ HPV genotypes 2,6, 11 and 16 were detected in 10.6% of cases of leukoplakia according to review done by Miller et al.⁴⁷ Lind et al reported that 7 of 13 HPV positive leukoplakias progressed to oral carcinoma within a 10 year period.⁴⁸

SQUAMOUS CELL CARCINOMA

SCC comprises nearly 95% of all oral carcinomas. Interestingly, an early report claimed a 5–6 fold increased risk of women with cervical cancer for the subsequent development of oral cancer.⁴⁹ Syrjänen and colleagues (1983) reported positive immunoperoxidase staining with anti-HPV serum in oral focal epithelial hyperplasia and oral squamous cell papillomas. The demonstration of papillomavirus antigens in premalignant lesions of the oropharynx provided first hints for a possible role of papillomavirus infections in oral squamous cell carcinomas.⁵⁰ The first unequivocal reports of specific HPV types in tongue and other oropharyngeal carcinomas appeared in 1985.^{51,52} Three of 13 carcinomas tested contained HPV 16 DNA, one was HPV 11 positive, and one contained HPV 27 DNA (initially labelled as variant HPV 2). In subsequent years a large number of studies confirmed these data, although the rate of positivity varied commonly between 25 and 60%.^{53,54,55} Miller et al., using in situ PCR to study 30 SCCs, showed that HPV is distributed in scattered foci throughout the epithelium, suggesting a non-clonal origin of the tumor.⁵⁶

CONCLUSION

Oral HPV infections has not been studied as extensively as cervical HPV infections. But studies have shown HPVs

association with benign, premalignant and malignant lesions. A hit and run theory has been proposed several times to explain the viral negative tumours. There is need to study the HPV infections in oral cavity more deeply. So, that in future HPV vaccines and cancer prevention can be done more effectively.

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