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

H Singh, P Kumar, A Kumar

Citation

H Singh, P Kumar, A Kumar. *Possible Role Of Human Papilloma Virus In Oral Diseases- An Update*. The Internet Journal of Infectious Diseases. 2010 Volume 9 Number 2.

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), leukolplakia, 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

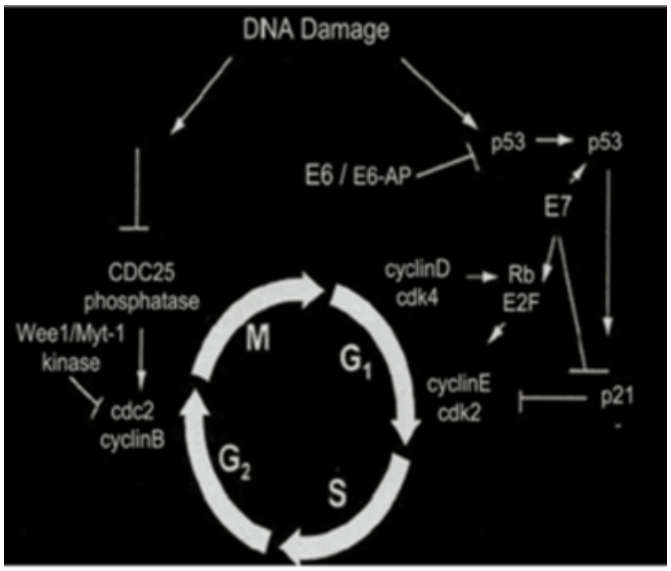
Human papilloma virus (HPV) Papilloma viruses are epitheliotropic viruses present in the skin and mucosa of several animals. In humans, more than 70 types have been described.[3] Mucosal and genital HPVs, consisting of about 30 types, are divided into low risk (HPVs 6, 11, 42, 43 and 44) and high risk (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 HPVinduced 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 PAPILLOMAS

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

Condyloma 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 condylomas 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 condyloma 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 shoeing 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 considerd 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.

References

1. Hausen HZ . Papilloma viruses in the causation of human cancers — a brief historical account. Virology 2009:384:260–65.
2. Miller CS, Johnstone B. Human papillomavirus as a risk factor for oral squamous cell carcinoma: A metaanalysis, 1982–1997. Oral Surg Oral Med Oral Radiol Endod 2001;91:622–35.
3. Zur Hausen H. Papilloma virus infections – A major cause of human cancers. Biochem Biophys Acta 1996;1288: 55–78.
4. Lowy DR, Kimbauer R, Schiller JT. Genital human papilloma viruses. Proc Natl Acad Sci 1994;91:2436–40.
5. Munoz N. Human papilloma virus and cancer: the epidemiological evidence. J Clin Virol 2000;19:1–5.
6. Milde LK, Reithdorf S, Loning T. Association of human papilloma virus infection with carcinoma of the cervix uteri and its precursor lesions: Theoretical and practical implications. Virchows Arch 2000;437:227–33.
7. McMurray HR, Nguyen D, Westbrook TF et al. Biology of human papilloma viruses. Int J Exp Pathol 2001;82:15–33.
8. Philips AC, Voudsen KH. Human papilloma virus and cancer: the viral transforming genes. Cancer Surv 1999;33:55–74.
9. Dyson N, Howley PM, Munger K et al. The HPV 16 E7 oncoprotein is able to bind to the retinoblastoma gene product. Science 1989;242:934–37.
10. Sellers WR, Kaelin WG. Role of Rb protein in the pathogenesis of human cancer. J Clin Oncol 1997;15:3301–12.
11. Scheffner M. Ubiquitin. E6-AP and their role in p53 inactivation. Pharmacol Ther 1998;78:129–39.
12. Munger K, Phelps WC, Bubb V et al. The E6 and E7 genes of the human papilloma virus type 16 together are necessary and sufficient for transformation of primary human keratinocytes. J Virol 1989;63:4417–21.
13. Villa LL, Schlegel R. Differences in transformation activity between HPV-18 and HPV-16 map to the viral LCR-E6-E7 region. Virology 1991;181:374–77.
14. Tang WK. Oncogenic human papilloma virus infection: Epidemiology in local high risk women. Hong Kong Dermatol Venerol Bull 2002;10:160-3.
15. Scully C, Prime S. Papilloma viruses: Their possible role in oral disease. Oral surf Oral Med Oral Pathol 1985;60:166-74.
16. Chang F, Syrjanen, Kellokoski J, Syrjanen K. Human papilloma virus infections and their associations with oral disease, J Oral Pathol Med 1991;20:305-10.
17. Coutlee F, Danielle R, Alex F, Eduardo F. The laboratory diagnosis of genital human papilloma virus infections. Cab J infect Dis Med Microbiol 2005;16:83-91.
18. Malloy C, Sherris MS, Herdman C. HPV DNA testing: Technical and Programmatic issues for Cervical cancer Prevention in low Resource settings. Path December 2000.
19. Abbey LM, Page DG, Sawyer DR. The clinical and histopathological features of a series of 464 oral squamous cell papillomas. Oral Surg 1980;49:419–28.
20. Frithiof L, Wersa J. Virus-like particles in human oral papilloma. Acta Otolaryngol Stockh 1967;64:263–66.
21. Jenson AB, Lancaster WD, Hartmann DP, Shaffer EL. Frequency and distribution of papilloma virus structural antigens in verrucae, multiple papillomas, and condylomata of the oral cavity. Am J Pathol 1982;107:212–18.
22. Stern E. Multiple weiche Warzen der Mundschleimhaut. Dermatol Wochen 1922;74:274–76.
23. Archard HO, Heck JW, Stanley HR. Focal epithelial hyperplasia: An unusual oral mucosal lesion found in Indian children. Oral Surg Oral Med Oral Pathol 1965;20:201-12.
24. Carlos R, Sedano HO.. Multifocal papilloma virus epithelial hyperplasia. Oral Surg Oral Med Oral Pathol 1994;77:631-5.
25. Eversole LR, Papanicolaou SJ. Papillary and verrucous lesions of oral mucous membranes. J Oral Med 1983;38:3-13.
26. Praetorius Clausen F. Histopathology of focal epithelial hyperplasia. Evidence of viral infection. Tandlaegebladet 1969;73:1013-22.
27. Beaudenon S, Praetorius F, Kremsdorf D, Lutzner M, Worsaae N, Pehau-Arnaudent G, Orth G. A new type of human papillomavirus associated with oral focal epithelial hyperplasia. J Invest Dermatol 1987;88:130–35
28. Syrjanen K, Syrjanen S. Papillomavirus infections in human disease. Wiley, New York, 2000, pp 1–615
29. Draganov P, Mateev, Botev I, Kalvatchev Z. Identification of multiple human Papilloma virus genotypes in a patient with oral condylomata Acuminata. Biotechnol. & Biotechnol. Jan 2006
30. Heidingsfield ML. Condylomata acuminata linguata. J Cutan Genitourin Dis 1901;19:226–34.
31. Wysocki GP, Hardie J. Ultrastructural studies of intraoral verruca vulgaris. Oral Surg 1979;47:58–62.
32. Lutzner M, Kuffer R, Blanchet-Bardon C, Croissant O. Different papilloma viruses as the causes of oral warts. Arch Dermatol 1982;118:393–99.
33. Jenson AB, Lancaster WD, Hartmann DP, Shaffer EL. Frequency and distribution of papilloma virus structural antigens in verrucae, multiple papillomas, and condylomata of the oral cavity. Am J Pathol 1982;107:212–18.
34. Jin YT, Toto PD. Detection of human papova virus antigens in oral papillary lesions. Oral Surg 1984;58:702–05.
35. Mincer HH, Jennings BR, Turner JE, Lee WB. Detection of human papova virus antigen in oral papillary lesions. Oral Surg Oral Med Oral Pathol 1985;59:516.
36. Syrjanen KJ, Pyrhonen S, Syrjanen SM, Lamberg MA. Immunohistochemical demonstration of human papilloma virus antigens in oral squamous cell lesions. Br J Oral Surg 1983;21:147–53.
37. Syrjanen K, Happonen RP, Syrjanen S, Calonius B. Human papilloma virus antigens and local immunologic reactivity in oral squamous cell tumours and hyperplasia's. Scand J Dent Res 1984;92:358–70.
38. Maitland NJ. Cox MF, Lynas C, Prime SS, Meanwell CA, Scully C. Detection of human papilloma virus DNA in biopsies of human oral tissues. Br J Cancer 1987;56:245-50.
39. Kashima HK, Kutcher M, Kessis T, Levin LS, De Villers EM, Shah K. Human Papilloma Virus in squamous cell carcinoma, leukoplakia, Lichen planus and clinically normal epithelium of the oral cavity. Ann Otol Rhinol Laryngol 1990;99:55-61.
40. Ackerman LV. Verrucous carcinoma of the oral cavity. Surgery 1948;23:670–78.
41. Jacobson S. Shear M. Verrucous carcinoma of the mouth. J Oral Pathol 1972;1:66–75.
42. Bohmfalk C, Zallen RD. Verrucous carcinoma of the oral cavity. Oral Surg 1982;54:15–20.

43. Walvekar RR, Chaukar DA, Deshpande MS, Pai PS, Chaturvedi P, Kakade A et al. Verrucous carcinoma of the oral cavity: A clinical and pathological study of 101 cases. Oral oncol 2009;45:47-51.
44. Syrjanen K, Syrjanen S. Papillomavirus infections in human disease. Wiley, New York, 2000, pp 1–615.
45. Pindborg JJ. Oral cancer and precancer. Bristol: John Wright & Sons ltd. 1980, pp 15-30.
46. Sand L, Jalouli J, Larsson PA, Hirsch JM. Human papilloma virus in oral lesions. Anticancer Res 2000;20:1183-8.
47. Miller CS, Dean KW. Human Papilloma Virus expression in oral mucosa, premalignant conditions and squamous cell carcinoma. A retrospective review of the literature. Oral Surg Oral Med Oral Pathol 1996;82:57-68.
48. Lind Po, Syrjanen SM, Syrjanen KJ, Koppong HS, Aas E. Local immunoreactivity and human papilloma in oral precancers and cancer lesions. Scand J Dent Res 1986; 94:419-26.
49. Newell GR, Krementz, ET, Roberts, JD. Excess occurrence of cancer of the oral cavity, lung, and bladder following cancer of the cervix. Cancer 1975;36 2155–58.
50. Syrjanen KJ, Pyrhone S, Syrjanen SM, Lamberg MA. Immunohistochemical demonstration of human papilloma virus antigens in oral squamous cell lesions. Br J Oral Surg 1983;21:147–53.
51. Löning T, Ikenberg H, Becker J, Gissmann L, Hoepfer I, Zur H. Analysis of oral papillomas, leukoplakias, and invasive carcinomas for human papilloma virus type related DNA J Invest Dermatol 1985;84:417–20.
52. De Villiers EM. Prevalence of HPV 7 papillomas in the oral mucosa and facial skin of patients with human immunodeficiency virus. Arch Dermatol 1989;125:1590.
53. Weinberger PM, Yu Haffty, Kowalski D, Harigopal M, Brandsma J, Sasakji C, Joe J, Camp RL, Rimm DL, Psyrri A. Molecular classification identifies a subset of human papilloma virus-associated oropharyngeal cancers with favourable prognosis. J. Clin. Oncol 2006;24:736–47.
54. Psyrri A, Di Maio D. Human papilloma virus in cervical and head and neck cancer. Nature Clin. Pract. Oncol. 2008:5:24–31.
55. Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, Viscidi R. Distinct risk factor profiles for human papillma virus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J. Natl. Cancer Inst. 2008;100:407–20.
56. Miller CS, Zeuss MS, White DK. Detection of HPV DNA in oral carcinoma using polymerase chain reaction together with in situ hybridization. Oral Surg Oral Med Oral Pathol 1994;77:480–86.

Author Information

Harkanwal Preet Singh, MDS
ITS Dental College

Prince Kumar, MDS
ITS Dental College

Ashish Kumar, MDS
ITS Dental College