A review literature on oral manifestations of human papillomavirus

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Abstract
Human papillomavirus (HPV) is one of the most common viruses affecting the skin, mucosal areas of the body, and also oral cavity. Oral HPV infection is usually benign-like squamous papilloma, condyloma acuminatum, and focal epithelial hyperplasia, etc. Oral HPV infection has been found to be associated with some other cases of oral cancer, but it is not the main risk factor for this kind of cancer. This review literature includes HPV genotypes, oncogenic risk, oral manifestations, and laboratory diagnosis.

Keywords: Human papillomavirus, laboratory diagnosis, oral manifestations, vaccinations

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Introduction
Human papillomavirus (HPV) is considered as the most frequently come up in the globe and diagnosed up to the minute annually. There may be certain diseases of oral cavities which are associated with Oral HPV infection. In United States, HPV is contemplated as the highest sexually transmitted infections (STIs). In STIs, the most common infected one is genital HPV with prevalence of around 6,000,000 worldwide, approximately 80% of sensual experienced male and female have been revealed in their lives to HPV. Oral sex behavior is a necessary benefactor of HPV in the mouth, mainly high risk, and initiates at an early age. Oral HPV infection is currently postulated to influence 25%-50% of the common people, according to diagnosing method. The immunity helps in clearing utmost of the HPV in their natural way in 1 and ½ years (about 91%), but once it persists may give rise to serious disorders. It is a main carcinogen which have been suggested rising in relation with tumors happening at many place of the body which includes the anus and genital tract, urethra, dermis, larynx, trachea and bronchial mucosa, nasal antrum, frontal, sphenoid, ethmoidal and maxillary sinuses, and oral mucosa. Although HPV has no particular treatment, treatable diseases are warts of genital region, neck region and other tumors.

Virology of HPV
HPV belongs to papillomaviridae family and is made of 56 nm deoxyribonucleic acid virus. The virus consists of uncoated, eccentric double stranded DNA with approximately 5600 nucleotide base pairs. More than 110 phenotypically dissimilar forms, with every kind having approximately 89% of them dividing a comparable DNA base pair homologically. Almost 50 HPV types infect the genital mucosa and 14 are recognized in most of the biopsies of exotic carcinoma of neck and are therefore considered as "extreme risk" or "carcinogenic." HPV and other lesions: HPVs “high-risk” are –16 and 18 and others – if constant, it may give on to cervical cancer and other genital areas. (i) 16 and 18 types of HPV are consider approximately 80% of all the cancers of cervix. (ii) HPV 16 and 18 consider approximately 30% wholly of the low-level potentially malignant lesions. (iii) 16 and 18 types of HPV are reported for an estimation of 50% of all high-level potentially malignant lesions. (iv) Infection with “less-risk” HPV types 6 and 11 and others – if constant, it may give on to cervical cancer and other genital areas. (v) Both extreme and less-risk types of HPV can happen cervical lesions and can be
done unusual smear Papanicolaou test.\(^8\) (viii) The extreme-risk types (mostly 16, 18, 31, 33, 35, 45, 52, and 56 types of HPV) are involved in cervical cancer. Among these, 16 and 18 types of HPV occur about 75% of neck cancers worldwide. (ix) The next highest incidence oncogenic type is HPV 45. It should be acclaimed that HPV 45 is more persistent in adenocarcinoma (15% of cases) than squamous cell carcinoma (SCC) (6% of cases). (x) Together, HPV 16, 18, and 45 cause 76% of SCC and 95% of adenocarcinoma. 31, 33, 35, 52, and 58 types of HPV are the next five highest oncogenic types together cause another 15% of all cervical cancers.\(^9\) (xi) In addition, 16 and 18 types of HPV together reported approximately 90.5% anal tumors and approximately half of all cancers of vulva and vagina. (xii) In male, anal disease as well as penile intraepithelial neoplasia happens and penile cancer accounts for 50%.\(^9\) (xiii) HPV can also cause non-genital diseases such as disease on the skin, mucosal surfaces of the cervical region, where it is mostly seen in oropharyngeal cancers.\(^10\) (xiv) HPV has a distribution worldwide. Worldwide incidence of the different HPV types has suggestions for the efficacy of HPV vaccines against HPV-induced oncogenesis. The use of in situ deoxyribonucleic acid hybridization as a strong device for the detection of certain HPV DNA sequences in oral biopsy and it is recommended vigorously.\(^{14}\)

### Immunopathogenesis

The exact process of accessing HPV into the cell is still not substantiated. It has been noted that the HPV capsid proteins take part as an important part in approaching host epithelial cell and transport of the viral DNA to the nucleus.\(^{11}\)

### HPV and Oral Cavity

Infections of oral HPV can be related to other dissimilar diseases of the mouth. Oral HPV may be considered to be difficulty rather than important diseases, except in several conditions such as the occurrence of oral squamous-cell carcinoma. Oral HPV lesions may show different clinical appearances, varied from benign lesions change into malignancy.

### Mode of Transmission

Transmission of HPV orally is ambiguous. HPV may be transmitted through sex (oral-genital contact) and nonsexual transfer of fomite such as sharing of wet towel, reason being HPV is extremely against noxious effects of dry and heat. Reason being HPV may initiate inactive subclinical infection, that they may have been received in early life, that is, developed at delivery from infected mother (cervix).\(^{12}\)

### Oral Manifestations of HPV

HPV involves in many kinds of benign oral lesions such as verruca vulgaris, squamous papilloma, focal epithelial hyperplasia, condyloma acuminatum, hairy leukoplakia, oral lichen planus (OLP), papillary hyperplasia, fibroma, and verrucous carcinoma have been discussed. Oral diseases and their genotypes are mentioned in Table 1. And HPV genotypes and oncogenic risk are mentioned in Table 2.

#### Squamous Papilloma

In most of the cases, HPV induced benign epithelial proliferation; some HPV subtypes have been recognized, mainly HPV 6 and 11. Their clinical features are papillary mass, and exophytic, measurement of \(<2\) cm in size. They are mainly stalk like based and consistency is soft. If they are in the form of white lesion, they are mainly single or many. It occurs on the palate, buccal mucosa, uvula, gingiva, and tongue.\(^{13}\)

#### Verruca Vulgaris (Oral Warts)

HPV groups which infect oral mucosal epithelium are mainly 2, 4, 6, or 11 types of HPV. Its clinical feature appears as papular to nodular with exophytic growth. The warts can be spiked, cauliflower-like, or raised with a flat surface, skin lesion around the mouth appears brownish. Lesion of oral mucosa shows pinkish appearance. Based may be stalk like or sessile. Preference sites include gingiva, palate, and lips. The prevalence has significantly elevated in the strong antiretroviral therapy period.\(^{13}\)

#### Focal Epithelial Hyperplasia (Heck’s Disease)

The most infectious of the papillary lesions affecting the oral cavity is Heck’s disease. At present, the etiology is said to be a subtype of HPV13 and 32. In Eskimos and American Indians, HPV is most commonly seen and in white Europeans are less. Related susceptible constituents are poor hygiene, poverty, and

### Table 1: Oral diseases of HPV and their genotypes\(^{23}\)

| Oral diseases | HPV types |
|--------------|-----------|
| Verruca vulgaris | 2, 4       |
| Condyloma lata | 6, 11      |
| Squamous papilloma | 6, 11 | |
| Focal epithelial hyperplasia | 13, 32   |
| Oral leukoplakia | 16, 18    |
| Verrucous carcinoma | 6, 11, 16 |
| Oral squamous cell carcinoma | 16, 18 |
| Laryngeal papilloma | 6, 11, 30 |
| Maxillary sinus papilloma | 57       |

### Table 2: HPV genotypes and oncogenic risk\(^{23}\)

| Risk type | HPV types |
|-----------|-----------|
| High      | 16, 18    |
| Intermediate | 31, 33, 35, 39, 45, 51, 52, 58, 59, 68 |
| Low       | 6, 11, 42, 43, 44 |
common lifestyle. Clinical features are mostly seen in young and mature people. This type of disease is characterized by confined; soft, broad based nodular growth of white color as compared to adjacent mucosal surface. Their common areas of collussion are buccal mucosa, lips, and tongue.[13]

**Condyloma Acuminatum**

They are mostly known as venereal or genital wart which happens frequently on genital region. Oral diseases may happen either through oral-genital sex or by auto-inoculation of genital lesions. It is caused by 6, 11, and 16 types of HPV. One of the four most common STDs is considered as condyoma acuminatum. Oral clinical feature appears as many tiny pinkish colored nodular growths which has tendency to unite to form papillomatous lesions. Frequently involving sites are palate, dorsum of tongue, gingiva, buccal mucosa, and alveolar ridge. The nodular growth multiply and combine to create soft, reddish or grey, broad or stalk such as based papillary growths. They enlarge quickly to create disconnected solitary or large groups of granular or cauliflower-like cancer.[13]

**Verrucous Carcinoma**

It is an alternative form of SCC, and has distinguished clinical behavior and morphology. They are mostly occurred on gingiva, buccal mucosa, and alveolar bone. Clinical features present as an exophyte showing warty cauliflower-like appearance, locally offensive but well distinguished. Etiopathogenesis of Orphans and Vulnerable Children (OVC) is ambiguous; but some studies showed that there are vigorous connections with tobacco use which includes alcohol, smoke and no smoke tobacco, and viral action related to HPV. In recent times, the relation between HPV and OVC by determining 6, 11, 16, and 18 types of HPV-DNA by restriction fragment analysis, polymerase chain reaction (PCR), and DNA slot–blot hybridization has been confirmed.[14]

**OLP**

It is a potentially malignant condition of unknown cause, which involves dermis and mouth. OLP has been related to a number of widespread systemic diseases such as diabetes mellitus and high blood pressure, and immunological diseases. The etiology of virus is also given by the current confirmations of HPV in more percentage of oral lesions.[21] Kashima et al. verified 4 of 22 OLP specimens which shows positive reaction in structural proteins of HPV.[15] Maitland et al. described that 88% (8/10) of OLP biopsies contain HPV DNA.[16] To date, 16 type of HPV related virus have been found in these lesions.

**Oral Leukoplakia**

It is a premalignant lesion with oral mucosal surface showing white patch or plaque like lesions seen in the oral mucosa. The etiology of oral leukoplakia is unclear. Tobacco and alcohol consumption are the exogenous agents that have been reported in the development of this lesion. In accordance with numerous studies, 16 type of HPV related virus has been establish in >90% of oral leukoplakia, disregarding of the level of epithelial dysplastic changes.[16] In accordance with Sand et al., 35% of the leukoplakia lesions were positive for 16 and 6/11 types of HPV.[17] According to Miller and Dean, 2, 6, 11, and 16 types of HPV were found in 11% cases of leukoplakia. Less risk of 6/11 type of HPV was found in 56% of HPV positive leukoplakia differentiate to 16/18 type of HPV (30%) and 2 type of HPV (16%). Nine of 15 HPV positive leukoplakia developed to oral cancer in a time of 10 years has been reported by Lind et al.[19]

**Oral Hairy Leukoplakia (OHL)**

It is benign, usual, symptomless, whitish, bilateral, often elevated, and non-scarable lesion which occurs in Human Immunodeficiency Virus (HIV) and AIDS patient on the lateral borders of the tongue. And also, Epstein-Barr virus seems to take part as an important role in etiopathogenesis. The precise molecular mechanisms are unknown. Numerous studies have suggested about the existence of Epstein-Barr virus.[20] HPV may occasionally present in the mouth OHL patients, even so it cannot be proven yet.[21]

**Oral SCC**

Head and neck SCC are a crucial source of illness and death worldwide mostly in India with the prevalence of >95% of SCC and 6th position among of all cancers in the world.[22] The connection between HPV and SCC was first explained by Zur Hausen in 1976, till then it has been considered as an absolute etiology for cervical cancer.[23] 25% of OSCC are associated with HPV cases are implicated by Syrjanen in 1983. [24] >95% of HNSCC and anal-genital carcinomas are caused by 16 type of HPV. It constitutes about 5% of cancer evolution, that is, > 6000 diagnosed cases daily and > 95% of oral cancers.[1]

**Oral Verrucous Carcinoma**

It is a form of SCC, started with wellcharacterized surface structure and clinical features. It is an unwonted tumor explained in 1948 by Ackerman as a malignancy that generally necessitate oropharynx, laryngeal mucosa, and lips. This is also termed as Ackerman’s tumor, pink papillomatosis, Buschke – Loewensteins, epithelioma, and carcinoma cuniculatum.[25] Frequently originated from 6, 11, 16, and 18 types of HPV.[26] The management plan is only resection or radiotherapy with resection, cytostatic drugs such as interferon alpha. Reoccurrence rate is more when only resection or radiotherapy is carried out.[24] Difference between oropharyngeal cancer HPV positive and HPV negative are mentioned in Table 3.
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**Table 3: Difference between oropharyngeal cancer HPV+ve and HPV –ve**

|                      | HPV positives                                                                 | HPV negatives                                                                 |
|----------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| **Age**              | Young people (between 30 and 50 years)                                        | Old people (between 50 and 70 years)                                          |
| **Risk factors**     | Oral sex, kiss, multiple sexual partners.                                     | History of tobacco/or alcohol consumption.                                    |
| **Incidence**        | Increasing                                                                    | Decreasing                                                                    |
| **Location**         | Base of tongue, amygdalae                                                     | Oral mucosa                                                                   |
| **Field cancerization** | No                                                   | Yes                                                                           |
| **Histology**        | Poorly differentiated basaoid                                                  | Clearly differentiated                                                        |
| **Stage of diagnosis** | T3-4, N2-3                                                                   | Variable                                                                      |
| **Biomarkers**       | Over-expressed p16, inactivation of p16 and pRb                               | Loss of p16; p53; and pRb mutation; cyclin- D1, EGFR (Epidermal growth factor receptor) and surviving overexpression. |
| **Chromosomal mutations** | Less frequent                                                              | Frequent                                                                      |
| **Prognosis**        | Very good increased sensitivity to radiotherapy and chemotherapy.            | Poor                                                                          |
| **Distant metastasis** | Rare                                                                  | Frequent                                                                      |
| **Second primaries** | Rare                                                                          | Frequent                                                                      |
| **5 years survival rate %** | 60–90                                                                 | 20–70                                                                         |

**Table 4: Laboratory investigations for detection of HPV**

|                      | Direct method                                                                 | Molecular methods                                                                 |
|----------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Light microscopy: Microscopic cellular features. Low sensitivity and does not indicate HPV types. | Non amplified technique: In situ hybridization, Southern blot, and dot blot. |                                                                                 |
| Electron microscopy: HPV particles can be identified. | Amplified technique: Target amplification, Hybrid captured technology. |                                                                                  |
|                      | **Drawbacks:** HPV types cannot be detected.                                 |                                                                                  |

**HPV Related with Pregnant Women**

Warts in genital area in pregnant women grow thoroughly as hypertrophy or hyperplasia, postulated because of effect in hormone, raised circulatory, and corresponding deficiency of immune system. C-section is suggested in instance of genital warts as transmission from an infected mother to infant is more than the infant delivered from an infected cervix. Many investigations have performed to find out whether HPV may directly transmitted from mother to infant by direct contact while delivery, or through rubbing the infant with infected towels, hands, bathing, etc. About 20% of 68 child gave birth from HPV infected mothers and 18% of 80 child from HPV non-infected mothers who are tested positive sometime during checkup. Thus, mothers who were HPV positive just after delivery check-up are nearly 6 times more risky to occur HPV positive than infants of correlated HPV negative mothers. The carcinogenic 16, 18, 31, 33, and 35 types of HPV are common, whereas 6 and 11 types of HPV are uncommon. The interconnection between HPV of oral cavity and pregnant is still to find out. Laboratory investigations for detection of HPV are mentioned in Table 4.

**Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM) Syndrome**

It is WHIM. It is related to raise in sensitivity to HPV. It is a rare autosomal dominant syndrome. There is an experience of HPV related SCC in two siblings with WHIM syndrome, which was described by Cipriani et al. Alteration in chemokine receptor CXCR4 revealed in a variation of progenitor and stem cells, but its part is not thoroughly distinguished.

**HPV Related to HIV**

In this, seropositive people manifested more incidence of infection in oral cavity with more carcinogenic chance of HPV, which rise in male more than female with aging, and infection by a protein named Virion Host Shutoff – 2, proven by Sikora et al. Chances of infection by more carcinogenic HPV types is 14 times more than HIV positive populations who performed sex orally with multiple people during the last year.

**Vaccination**

In India, protective vaccine against HPV is accepted presently. A quadrivalent vaccine, named Gardasil® (US) is efficacious in opposition to 6, 11, 16, and 18 types of HPV. The vaccine deploys large capsid protein L1 of certain HPV types, which has the capacity to self-build into microorganism-like molecules. Contamination is protected by initiation of counteracting antibodies in opposition to L1. Gardasil is presently prescribed...
in a sequence of 3 IM injections. While a double valency vaccine that prevents in opposition to HPV16 and 18 are accessible. In India, use of Cervarix (Belgium) has still not accepted. Both the vaccines assign prevention in opposition to cervical malignancy.[30]

Conclusion

Recently HPV has approved as an important correlation with cervical malignancy. Today HPV infections orally have shown relation between several tumors and HPV infection and are incontrovertible. Carcinogenic HPV is related with oral cancers, but its incidence differs generally in dissimilar reports. Many studies reported that, there is possibility that use of tobacco and alcohol consumption may interconnect with HPV infection to raise in chances of forming oral malignancy. Hence, HPV infections orally need to be study or investigate thoroughly to guide us to conduct subsequent cancer prevention programs, which include vaccination for oral HPV.

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