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HPV and Oral Health

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Abstract: ***The HPV virus can cause various medical issues in humans, leading to different kinds of lesions in various parts of the body, including the mouth. In particular, the virus has been identified as a major factor in the increased incidence of cancer in certain parts of the oral cavity, such as the tonsils, oropharynx, and base of the tongue. This has had a significant impact on the occurrence of oropharyngeal and oral cavity cancer in many regions, including Asia, Europe, North America, and Oceania.***

Keywords: Human papillomavirus (HPV), Oral Health, Oral Cancer, Verruca vulgaris, Squamous papilloma, Condyloma acuminatum, Multifocal epithelial hyperplasia, Squamous Cell Carcinoma, Oral Lesions, HPV Vaccine.

1. Introduction

The Humanpapilloma virus (HPV) is the primary cause of the most prevalent sexually transmitted infections. It is believed that around two - thirds of individuals who engage in unprotected sexual activities with someone carrying HPV will contract the virus [1].

As HPV has a preference for epithelial tissue, it has the potential to affect both the skin and mucosa. It can cause a variety of different types of damage, ranging from asymptomatic infections and benign warts to more severe and invasive forms of injury. HPV infections have been detected in many different areas of the body, including the genital and anal tracts, urethra, upper respiratory tract, tracheobronchial lining, nasal cavities, and oral cavity. Depending on the diagnostic approach used, the prevalence of HPV infections in the oral mucosa can range from 1% to 43% in the general population and in some cases, it may even be linked to the development of oral cancer [1].

In female, it can lead to cervical cancer, as well as cancer in the vulva, vagina, throat and mouth. In males, it may lead to cancer in the anus, penis, throat and mouth [2].

HPV has been associated with the development of oropharyngeal cancers – cancers that emerge in the neck, head and in the mouth, affecting the tonsils, base of tongue, back of throat and walls of pharynx. If left untreated, oral cancer can be life - threatening [2].

Virion Structure of HPV

The human papillomavirus has a non - enveloped icosahedral capsid with a diameter of 55 nm that encloses a circular double - stranded DNA consisting of around 8, 000 base pairs. The DNA genome has only one of its strands transcribed, and it has 9 - 10 open reading frames with regions that could potentially code for proteins [3].

HPV Strains and Cancer Risk

There are almost 200 strains of HPV, and around 40 of them can infect the genital and oral mucosa. Out of these 40, nine strains have the potential to cause cancer, with HPV - 16 being the strain most likely to cause oropharyngeal cancer. Recent research has shown that 7% of Americans between the ages of 14 and 69 have oral HPV infection, and there has been an increase in the number of people with HPV over the past three decades, with more men than women being affected [4].

HPV is a small virus with double - stranded DNA that can invade epithelial and cutaneous tissues, and its prevalence in the adult population's oral cavities is 7.3%. It can spread through high - risk sexual behavior, such as oral sex, which can lead to the development of oropharyngeal cancer, especially in younger people. This type of cancer can occur without the use of tobacco or alcohol. Studies have revealed that 80% of oropharyngeal cancers occur due to HPV spread, and HPV - 16 is the most common type of HPV - related cancer. The involvement of HPV - 16 and HPV - 18 is 73% (460, 000 cases), while the involvement of HPV - 6, HPV - 11, HPV - 16, HPV - 18, HPV - 31, HPV - 33, HPV - 45, HPV - 52, and HPV - 58 is 90% (570, 000 cases) [5].

HPV Classification

The various types of HPV fall into two main categories:

Cutaneous HPV: HPV can cause skin lesions like common or vulgar warts, which are commonly found on the hands and feet and appear as white - greyish or brown flat or raised papules. Types 1, 2, 3, 4, and 7 are the most frequently associated genotypes with warts. Epidermodysplasia verruciformis (EV) is a rare familial dermatosis caused by cutaneous HPV genotypes 5, 8, 9, 12, 14, 15, 17, 19, 20, 47, and 49. This condition is characterized by the dissemination of multiple papular and macular elements, typically appearing in childhood and can lead to a neoplastic transformation within 20 - 30 years of onset. This transformation can result in the development of first bowenoid carcinoma in situ and subsequently squamous cell epithelioma, which can manifest as flat warts and reddish macules, and even progress to squamous cell carcinomas.

Mucosal HPV: It is responsible for benign mucous lesions, such as sharp and flat warts that typically appear in the female and male genitalia, the urethra, the perianal area, and

the anus. These infections are usually caused by genotypes 6 and 11 of HPV. [6]

Mucosal HPV further divided into three types:

- High - risk HPV (HR - HPV) genotypes (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82),
- Putative high - risk HPV (pHR - HPV) genotypes (types 26, 53, and 66), and
- Low - risk HPV (LR - HPV) genotypes (types 6, 11, 40, 42, 43, 44, and 70) [7].

Risk Factors

The study found that both smoking and having multiple oral sex partners were separate risk factors for oral HPV infection and had similar odds ratios. Additionally, the results suggest that poor oral health is another risk factor for oral HPV infection, as all four measures of oral health showed associations with oral HPV infection in univariable analyses [8].

Route of Transmission

The infection can be transmitted through three different modes of contact:

1) There are various ways that HPV can be transmitted between different mucosal sites. These include autoinoculation within one individual as well as transmission between individuals. Transmission between individuals can occur through perinatal transmission, or through sexual contact involving different techniques of orogenital sex or deep kissing.
2) Indirect contact can occur through fomites such as contaminated medical instruments, utensils, or linen.

Perinatal transmission of HPV can occur when the virus is passed from the mother to the fetus through the placenta or umbilical cord blood, during birth, or through breast milk. This type of transmission is also referred to as vertical transmission and can occur during different stages such as in utero through ascending infection, during vaginal delivery, or during a caesarean section. The virus can also be transmitted from the male sexual partner during periconceptual transmission. [9]

In order to infect the oral cavity, HPV enters through the basal layer of the epithelium via any existing epithelial wounds. Poor oral health, which can lead to ulcers, chronic inflammation or mucosal disruption, may increase an individual's susceptibility to HPV infection and also increase their likelihood of spreading the infection to others. [9]

Oral Signs and Symptoms

HPV infection range from asymptomatic to visible lesions, which can be benign or malignant:

Benign HPV Lesions

- Verruca vulgaris
- Squamous papilloma
- Condyloma acuminatum
- Multifocal epithelial hyperplasia

Verruca vulgaris (Common wart):

Cutaneous HPV infection often presents as verruca vulgaris, which accounts for around 70% of warts. The incidence is highest in teenagers aged 12 - 16, with an estimated 10% of children and young adults affected. [10]

In the oral cavity, common sites of involvement include the palate, vermillion border, labial mucosa, and anterior tongue. [10]
Oral lesions are believed to be the result of auto - inoculation, which explains why the anterior aspects of the oral cavity, especially the lower lips, are often affected. [11]

The clinical presentation typically includes painless lesions measuring 2 - 5mm in diameter with pronounced white, papillary projections due to marked hyperkeratosis. [11]

Solitary lesions are commonly observed, but it's also possible for multiple sites of infection to occur simultaneously or in clusters. [10]

It is Commonly associated with HPV 2, 4 [10].

Histologically, verruca vulgaris is characterized by a proliferation ofhyperkeratotic stratified squamous epithelium forming finger - like projections with connective tissue cores. The elongated rete ridges converge towards the center of the lesion, creating a "cupping" effect. A granular cell layer with coarse, clumped keratohyalin granules is prominently displayed (known as hypergranulosis), and abundant koilocytes can be found in the superficial spinous layer [12].

The possible diagnoses to be considered include focal epithelial hyperplasia, oral squamous papilloma, oral lichen planus, oral leukoplakia, oral verrucous carcinoma, and oral squamous carcinoma [13].

Treatment may not be necessary for the majority of oral warts since they are self - limiting. However, patients may seek treatment due to aesthetic concerns or bite - related injuries. Several treatment methods are available, including liquid nitrogen cryotherapy, electrosurgery, surgical removal, Trichloroacetic acid, and Imiquimod. [14]

Oral squamous papilloma:

Squamous cell papilloma is a benign hyperplastic exophytic localized proliferation with a rough or cauliflower - like appearance. It can be either pedunculated, meaning it has a stalk, or sessile, meaning it is flat with no stalk. Pedunculated lesions consist of a group of finger - like projections and can appear either white or mucosal, depending on the amount of keratinization present [15].

The color of the growth can range from white to pinkish - red, depending on the amount of keratinization present. Typically, these growths are small, measuring a few millimeters to less than 1 cm in diameter, but in rare cases, they can grow up to 3 cm in diameter. [15]

Squamous cell papilloma (SP) is a common growth and the most prevalent non - cancerous oral epithelial condition in both children and adults, with adults having the highest occurrence [10].

The palate and tongue are the most commonly affected areas, any part of the mouth can be involved [10].

Squamous cell papillomas are typically caused by HPV - 6 and 11 and are not considered precancerous [11].

Histologically it is characterized by keratinized stratified squamous epithelium that surrounds fibrovascular connective tissue cores. In some instances, there may be basilar hyperplasia and elevated mitotic activity, which should not be confused with low - grade dysplasia. Additionally, koilocytes, which are abnormal cells with a halo - like appearance, may be seen in the superficial layers of the growth [16].

Oral squamous papilloma may bear a resemblance to other conditions such as verruca vulgaris, condyloma acuminatum, verruciform xanthoma, or multifocal epithelial hyperplasia [16].

The preferred method of treatment is surgical removal, which should involve a clearance of at least 1 mm from the base to the submucosa depth. Alternative treatments include electrocauterization, cryosurgery, laser surgery, and interferon injections. The effectiveness of topical cidofovir as a treatment for squamous cell papilloma in HIV - positive patients requires further research. Some studies have suggested that topical applications of salicylic acid and vitamin A may be helpful in treating the condition [15].

Condyloma acuminatum:
Condyloma acuminatum typically appears as warts in the anogenital region and is the most frequently reported sexually transmitted infection in both the United Kingdom and the United States. Although these growths are rare in the oral cavity, the presence of lesions in both the genital and oral areas suggests that sexual transmission may be a factor. However, it is also possible for the infection to spread through contact with contaminated objects. The condition is most commonly observed in adults, with a higher incidence in the third and fourth decades of life [10].

Patients with uncomplicated condyloma typically do not experience symptoms. Their growths appear as soft, pedunculated papules that are approximately 2 to 3 mm in diameter. These pink nodules may combine to form cauliflower - shaped clusters and may manifest as a single mass or multiple growths [17].

Condyloma acuminatum has been linked to the HPV 6 and 11 [17].

Histologically these growths are identified by the presence of numerous koilocytes, bulbous rete pegs, hyperplasia, and mild parakeratosis [17].

Treatment for Condyloma acuminatum consists of surgical removal, electrocautery, cryosurgery, laser ablation, photodynamic therapy, Mohs microsurgery, and topical application of cytotoxic agents such as podophyllum resin, 5 - fluorouracil, or trichloroacetic acid. Due to the tendency of these lesions to recur, patients usually require ongoing follow - up care and additional treatment [18].

Focal epithelial hyperplasia (Heck's disease):
FEH, also known as Heck's disease, is a rare oral mucosa disease that is commonly observed in children or young adults living in areas with low socioeconomic status and who are immunosuppressed.

FEH is characterized by the presence of numerous painless nodules or papules with varying sizes (1 mm to 1 cm) found on the lips, tongue, buccal mucosa, and palate.

The primary viruses associated with FEH are HPV 13 and HPV 32.

Histologically, FEH presents with parakeratosis, acanthosis, elongation of rete ridges (bronze age battle - axe appearance), and the presence of koilocytes, as well as other cellular modifications indicative of viral infection, such as cells with nuclear degeneration (mitosoid cells) [19].

The differential diagnosis of focal epithelial hyperplasia includes several conditions such as condyloma acuminatum, verruca vulgaris, papilloma, irritation fibroma, verruciform xanthoma, juvenile papillomatosis, and various syndromes like multiple endocrine neoplasia, neurofibromatosis, tuberous sclerosis, Cowden syndrome, and Goltz - Gorlin syndrome. [20]

In most cases, no treatment is necessary unless the lesions are bothersome or unsightly or if there is a risk of accidentally biting them. If treatment is deemed necessary, options may include removal of the lesions through methods such as excision biopsy, cryotherapy, CO2 laser, electrocoagulation, or electrodessication. If there is widespread involvement, topical or systemic interferon can be effective. Other treatment options include levamisole, topical podophyllin resin, or vitamins. [21]

Potentially Malignant HPV Lesions
The most common Potentially malignant HPV lesions (PMOD) are

- Oralleukoplakia,
- Proliferative verrucous leukoplakia,
- Oral erythroplakia
- Oral lichen planus. [22]

Oral Lichen Planus:
OLP is a chronic inflammatory disease that affects approximately 1% of the population and is believed to be mediated by T - cells, although its exact cause is not well understood. On a histological level, the disease is characterized by a thickening of the outer layer of skin (hyperkeratosis), a break - down of the interface between the oral epithelium and the connective tissue beneath it, and a dense infiltration of lymphocytes. There is some debate about whether or not HPV is involved in the development of OLP; while some studies suggest a link between the two, others do not. In cases where high - risk HPV types (such as HPV16 and HPV18) are present, there is a risk of OLP progressing to cancer, although the extent to which HPV contributes to this process is not fully understood, and other factors such as smoking and oral hygiene may also play a role [23].

Oral Leukoplakia:
Oral leukoplakia (OL) is a rare lesion of the oral mucosa that has the potential to become cancerous. In 1978, Kramer and colleagues defined it as a white patch or plaque that cannot be identified clinically or histopathologically as any other disease. OL is the most common pre - cancerous lesion of the oral mucosa and is more prevalent in males. Clinically, OL can be classified as either homogeneous or non - homogeneous leukoplakia. Homogeneous leukoplakia is further classified as flat, corrugated, wrinkled, or pumice - like, while non - homogeneousleukoplakia is classified as verrucous, nodular, ulcerated, or erythroleukoplakia. [24] The fundamental microscopic features of oral LKP involve hyperkeratosis, which can either be of the ortho - or parakeratotic type, and acanthosis of the epithelium. The degree of chronic inflammatory infiltrates in the lamina propria varies. Epithelial dysplasia may also occur to varying degrees. The most important microscopic features of dysplasia include the loss of polarity of basal cells, an increased nuclear cytoplasmic ratio, irregular epithelial stratification, an increased number of abnormal mitotic figures that are present in the superficial epithelium, cellular and nuclear pleomorphism, and the keratinization of single cell groups. [25]

Malignant HPV Lesions
The most common malignant neoplasm of the oral cavity is squamous cell carcinoma.

Squamous Cell Carcinoma (SCC):
The involvement of the virus in causing cancer in the oral cavity is a topic of much debate. According to Syrjanen et al., the prevalence of HPV infection was significantly higher in individuals with SCC oropharynx and oral SCC than in those with healthy mucous membranes, particularly in relation to HPV 16. This suggests that HPV 16 infection is a significant factor in the development of oropharyngeal tumors. In fact, up to 70% of oropharyngeal tumors are believed to be HPV positive (HPV 16) in comparison to the healthy mucosa [26].

Oropharyngeal squamous cell carcinoma, also known as throat or tonsil cancer, is a type of cancer that affects the middle part of the pharynx, specifically the oropharynx. This area stretches vertically from the soft palate to the upper portion of the hyoid bone and includes the posterior and lateral pharyngeal walls, tonsils, base and posterior one - third of the tongue, and soft palate. HPV 16 is responsible for almost 90% of HPV - positive oropharyngeal cancers, with higher prevalence observed in males. The most common causes of oral HPV infection are oral sex and open - mouthed kissing. HPV - associated OPSCC is often found in the tonsils and base of the tongue.

The most common symptoms of OPSCC are persistent sore throat, dysphagia, odynophagia, dysarthria, presence of a lump in the neck, and otalgia. Patients may also experience hoarseness, unexplained weight loss, and hematemesis. Physical examination of the oropharynx may reveal ulcers or red/white patches on the base or posterior one - third of the tongue, posterior and lateral pharyngeal walls, soft palate, or tonsils.

Histologically, the accumulation of genetic changes leads to the progression of mild and moderate dysplasia to severe dysplasia/carcinoma in situ. In most HPV - positive oropharyngeal cancers, the tumor originates deep inside the tonsillar crypt epithelium. To diagnose OPSCC, other conditions with similar presentations, such as actinic keratosis, erythroplasia, lichen planus, leukoplakias, lichenoid lesions, oral candidiasis, tonsillitis, and traumatic lesions, need to be excluded.

Treatment options for OPSCC include surgery and radiotherapy. For small tumors that have not advanced, surgery or radiotherapy can be used primarily. However, a combination of surgery and radiotherapy is used if the disease has advanced or the tumor is larger. Minimally invasive procedures such as transoral laser microsurgery (TLM) have been found safe and effective as a first - line treatment modality for oropharyngeal carcinomas. Other resection methods include transoral robotic surgery, transoral video laryngoscopic surgery, transoral ultrasound surgery, and endoscopic laryngopharyngeal surgery. [27]

Molecular Methods for HPV Detection
Detecting HPV accurately can be challenging since the virus is unable to reproduce in tissue culture. This means that molecular biology techniques are often necessary for precise detection. HPV has a double - stranded DNA genome of approximately 8000 base pairs and a known physical structure and gene organization. As a result, nucleic probe technology is typically the preferred method for detecting HPV in clinical specimens [28].

There are three main tests:

1) Nucleic acid - hybridization assays
Initially, techniques such as Southern blotting, in situ hybridization, and dot - blot hybridization were utilized to identify HPV infection in cervical samples through radio - labeled nucleic acid hybridization assays. Although these methods yielded useful data, they also had limitations. Direct - probe approaches like these had a low sensitivity, needed large quantities of purified DNA, and were laborious.

2) Signal - amplification assays
Currently, only two diagnostic testing methods have been approved by the FDA (Food and Drug Administration) for use in the United States. These are the Digene® HPV test, which employs Hybrid Capture® 2 (hc2) technology, and the Cervista® HPV HR assay. [28]

3) Nucleic acid - amplification methods

- Microarray analysis
- Papillo Check®
- Polymerase chain reaction (PCR
- PCR - RFLP
- Real - time PCR
- Abbott real - time PCR
- COBAS® 4800 HPV test
- HPV genome sequencing
- CLART® human papillomavirus 2
- INNO - Lipa
- The Linear array®
- Clinical arrays® HPV
- Microplate colorimetric hybridization assay (MCHA)
- PreTect® Proofer
- APTIMA® HPV Assay [28]

HPV Vaccine

The Advisory Committee on Immunizations Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommends HPV vaccination as a means of preventing new HPV infections and HPV - associated cancers and other illnesses.

According to the FDA three vaccines protect against HPV:

- A 9 - valent vaccine that protects against HPV types 6 and 11, types 16 and 18 and types 31, 33, 45, 52, and 58.
- A quadrivalent vaccine (HPV4) that protects against types 6, 11, 16, and 18
- A bivalent vaccine (HPV2) that protects against types 16 and 18

Only the 9 - valent vaccine is commonly used.

The process of creating HPV vaccines involves utilizing recombinant DNA technology to produce the major capsid protein (L1) of HPV. These L1 proteins then spontaneously organize into noninfectious and nononcogenic virus - like particles (VLPs). [29]

To protect against HPV infections that may lead to cancer later in life, the CDC recommends HPV vaccination for all preteens, starting at age 9, and specifically recommends vaccination at ages 11 - 12 with two doses given 6 to 12 months apart.

The CDC recommends that preteens aged 11 - 12 receive two doses of the HPV vaccine, given 6 - 12 months apart. The first dose is typically given at age 11 - 12, but can be started as early as age 9. If the first dose is given before the age of 15, only two doses are needed. However, teens and young adults who start the series later, between the ages of 15 - 26, require three doses. Children aged 9 - 14 who receive two doses less than 5 months apart will also need a third dose, as will individuals aged 9 - 26 with weakened immune systems. Those over 26 years old are not recommended to receive the vaccine [30].

The HPV vaccine can be administered to individuals between the ages of 27 and 45 who did not complete the full vaccine series earlier. However, the benefits of the vaccine in this age group are reduced as they are more likely to have already been exposed to HPV [31].

2. Conclusion

In conclusion, there is a growing body of evidence suggesting a link between HPV and oral health. HPV has been found to be a risk factor for oral lesions such as Verruca vulgaris, Squamous papilloma, Condyloma acuminatum, Multifocal epithelial hyperplasia and oral cancer, and its prevalence is increasing. It is important for individuals to take steps to protect their oral health, such as practicing good oral hygiene and getting regular dental check - ups. Additionally, the HPV vaccine is highly effective in preventing HPV - related diseases, including oral cancer. By being aware of the risks associated with HPV and taking appropriate measures to prevent it, individuals can protect their oral and overall health. Further research is needed to better understand the link between HPV and oral health, and to develop effective strategies for prevention and treatment.

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