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HUMAN PAPILLOMA VIRUS - ORAL INFECTION –A REVIEW

Oral Pathology

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ABSTRACT

Human papilloma virus is the most common sexually transmitted infection and persistent HPV is associated with high risk of cervical cancer, genital warts and also oral mucosa. The benign clinical manifestation of HPV infection are oral papilloma / condyloma and focal epithelial hyperplasia. The association between Human papilloma virus [HPV] types and oral lesions have been shown in many studies. The purpose of the study is to highlight the persistent infection of HPV (which tend to become malignant), transmission of HPV, oral signs and symptoms of infection and their treatment.

KEYWORDS

Human papilloma virus ,oral infection, transmission of HPV, malignancy of HPV infection

INTRODUCTION

Human papilloma virus [HPV] which belongs to the PAPOVA VIRUSES group. The HPV virus has a etiological role in benign and malignant neoplasm in both animals and humans. These papilloma virus were first to be implicated in the etiology of any human neoplasia. These viruses appear to replicate in the layer of stratified squamous epithelium. More than 100 HPV types have been identified their individual types are associated with different lesions. In humans HPV were first detected as etiologic agent in common skin warts or verruca vulgaris (squamous cell carcinoma) by Shope in 1933, the condition is said to be infectious [1]. Papillomaviruses has a strict species specificity with a broad genotypic diversity. The ancient papillomaviruses with mucosal tropism started developing some 90 million years ago [2]. The human papilloma virus (HPV) is a small-sized DNA virus (diameter 50-55 nm) without envelope, which is resistant to heat, acids, and ether. Currently, over 120 types of HPV have been identified, 16 different genera based on biological properties and the organization of genome have been identified [3–5]. Papilloma viruses have a soaring tropism for stratified squamous epithelial cells and replicate only in differentiating epithelial cells of the skin and mucous [4]. The human papilloma virus have include both low-risk and high-risk HPVs [7]. The low-risk mucosal HPVs, such as HPV6 and HPV-11, cause benign papilloma/condyloma, whereas the high-risk mucosal HPVs, such as HPV-16 and HPV-18, cause squamous intraepithelial lesions that can be progress to squamous cell carcinoma in the head and neck region and anogenital tract.

Transmision Of HPV

Unlike the HPV infections in skin, mucosal HPV infections have been regarded as the sexually transmitted infections, despite the fact that Betapapillomaviruses (HPV) have been found in virgins, infants, and children, in both oral and genital mucosa. This implies the non-sexual mode of transmission [13, 14, 15, 16, 17]. Perinatal transmission has also been regarded as the most likely explanation for the presence of HPV in newborns. Several studies have shown that children born to the HPV-positive mothers have the higher risk of becoming HPV positive [18, 19, 20, 21, 22, 23, 24,25].

Transmission of the oral infection occurs with two different methods of contact: (i) Direct horizontal contact (saliva-saliva or genital mucous membranes during sexual intercourse): oral sexual contact is certainly one of the most frequent ways of transmission of the papilloma virus; a relationship have been demonstrated between the presence of HPV in the oral cavity and the age of onset of sexual activity in the young; the presence of oral HPV is also more evident in couples who practice oral sex , compared to couples in which only genital sex is practiced; a 10 times higher risk of the oral HPV infections were then calculated in patients who have had more than 20 sexual partners in their lifetime compared to individuals with fewer than 3 partners [26]

(ii) Indirect contact (through contaminated medical instruments, utensils, or linens)

SIGNS AND SYMPTOMS

Oral Signs and Symptoms

(i) Subclinical infection: the presence of HPV in a clinically normal mucosa is found in about 10% of subjects, which represent a potential reservoir for the infection transmission

(ii) Squamous papilloma: it is associated with HPV 6 and 11, and it is the most common manifestation of oral HPV infection; it is localized on the nonkeratinized mucosa (lingual belly, soft palate) or keratinized (hard palate) and appears as an exophytic neoformation with a cauliflower surface. From the histological point of view, it is composed of a connective axis with a villous and papillary morphology (arborescent appearance) covered by a paving epithelium which presents a notable hyperkeratosis and acanthosis (verrucous hyperplasia); at the cellular level, there is a clear vacuolization of the cells of the spinous layer (koilocytosis) characteristic of the HPV infections

(iii) Verruca vulgaris: it is associated with HPV 2 and 4, is rare in the oral mucosa, and is localized at the level of the keratinized mucosa (lingual dorsum, adherent gingiva); it is found more frequently in the children, as a consequence of self-inoculation, and is generally self-limited, resolving in less than 2 years

(iv) Condyloma acuminata: it is associated with HPV 2, 6, and 11, and it is extremely contagious and is often found associated with genital warts. It is localized on nonkeratinized mucosa (lingual belly, soft palate) and have a wider implant base than papillomas and warts and a more pinkish color as it is often devoid of hyperkeratosis

(v) Squamous cell carcinoma: the role of virus in carcinogenesis of the oral cavity is highly controversial, but it is now believed that HPV infection, in particular HPV 16, is important in the pathogenesis of oropharyngeal cancer (cancer of the back of the mouth); in fact, oropharyngeal tumors are 70% HPV positive (HPV 16), and compared to the healthy mucosa, HPV infection in these tumors is almost 13 times more frequent [27-29]. There is

also a whole literature that reports the existence of a significant relationship between the incidence of oropharyngeal cancer and "sexual behavior" (habit of oral sex and the presence of multiple partners).

Today, it is hypothesized that the tumor is associated with HPV infection follows a different patterns compared to the "classic" tumor of the oral cavity which is generally linked to known risk factors (smoking and alcohol) [30–33].

Table1 Oral HPV Signs [34]

Definition	Clinical signs	Description	% of HPV infection
Subclinical	Normal mucosa	No clinical or histopathological lesions HPV-DNA revealed by the molecular biology technique	0-81
Clinical	Benign lesion Potentially malignant lesion	Squamous cell papilloma Oral leukoplakia Oral erythroplakia Oral lichen planus	5-62% 22-100% 0-54% 11-60%
Associated	Malignant lesion	Leukoplakia proliferative wart Squamous cell carcinoma Verrucous carcinoma	0-89% 0-38% 0-7.7%

HPV Oncogenesis In Human Cancer

Persistence infection in target epithelial cells drives the molecular hallmark of cancer and directly affect the cell growth by (i) integrating the host cell DNA which result in over expression of viral protein E6 and E7 from high risk HPV types. (ii) E6 and e7 viral protein cause loss of p53 and pRB, the two cell protein with tumor suppressor properties .Thus the brakes in cell proliferation are removed, permitting the uncontrolled proliferation. (iii) These viral protein activate cyclin A and E , and inactivate CDKIs, thus permitting further cell proliferation (iv) these viral proteins mediate and degraded BAX, a proapoptotic gene ,thus inhibiting apoptosis (v) these viral proteins activate telomerase, immortalizing the transformed host target cells[1].

HPV infection, in particular HPV 16, is important in the pathogenesis of the oropharyngeal cancer; oral carcinoma accounts for more than 90% of all malignant neoplasms of the mouth. It most frequently affects individuals over fifty years of age and males to a greater extent than females in a ratio of about 2:1 [8–11]. Oral HPV infections have been linked to sexual behavior, but recent evidence showed their horizontal, mouth-to-mouth transmission. Most the HPV infections in infants are acquired vertically from the mother during the intrauterine period, during delivery, or later via saliva[6]. In rare cases, the virus that is localized in some of the cells of oral mucosa changes them and transforms them into malignant tumors[12]. However, there is a high association of patients with oral carcinoma with the papilloma virus infection. For this reason, early diagnosis of the oral infections becomes essential.

Detection Of HPV

The biopsy remains one of the most usual method of oral sampling. Other methods like oral scrapings, oral rinse sampling can be used. Lately, the oral rinse was proposed as method of cytological sampling more efficient than the superficial brushing/scraping of oral mucosa in terms of DNA yield, quality and stability, as well as acceptability by the sample donor [35, 36]. A recent meta-analysis on the oral and oropharyngeal cancers showed that representative biopsy from the lesion resulted in the highest HPV detection rates especially when PCR was used (29.8% versus 38.1%) [37]. Though there are many methods to detect HPV infection, there is no gold standard method for the HPV detection.

Prevention

To date, three preventive HPV vaccines have been developed and the clinical evaluation in randomized clinical trials were done [42]: (i) monovalent HPV 16 vaccine (manufactured by Merck, Sharpe & Dome, Whitehouse Station, NJ, USA); (ii) quadrivalent vaccine containing L1 protein of HPV 6, 11, 16 and 18 (Gardasil®, produced by the same manufacturer); (iii) bivalent vaccine containing L1 of HPV 16 and 18 (Cervarix®, produced by GlaxoSmith, Rixensart, Belgium).

Both the HPV vaccines need three doses, the first at day 1, the second at month 1 for bivalent vaccine and month 2 for quadrivalent one, and the third at the month 6 [43]

Treatment

As discussed with respect to genital HPV infection, also in oral cavity HPV subclinical infection does not need a treatment since any tested antiviral drugs (e.g. acyclovir, ribavirin) have been demonstrated were able to eliminate the infection [38]

If HPV-related lesions is present, the treatment is based mainly on surgery, since local or systemic applications of medications (cytotoxic or immunomodulatory drugs) were extensively tested in head and neck region only for RRP, as above reported, and not for oral mucosal lesions. Recently, an experimental study has tested a bio-adhesive patch system releasing imiquimod for the topical treatment of dysplastic and neoplastic lesions (dosecontrolled topical delivery) that may able to extend the clinical uses of this immunomodulatory agent to the treatment of potentially malignant lesions conditions of oral as well genital mucosa recognized to be HPV- infected [39]. Surgical therapy. The excision of the lesions, associated with HPV DNA test (usually performed in epithelial cells collected by oral rinse/brushing before surgery or in formalin-fixed/paraffinembedded or fresh frozen histological samples) could be carried out after local anaesthetic agent by traditional cold knife, quantic molecular resonance (QMR) scalpel [40] or electro-surgery. The last technique could influence negatively the histological examination, especially in presence of small sized lesions, because of cauterization of margins of the samples. Likewise, since the laser ablation of HPV-related lesions is bothering, the histological diagnosis is essential to distinguish each HPV-related lesion from the others HPV-unrelated with similar clinical presentation and to identify any grade of epithelial dysplasia, if present. In the presence of lesions sized more than 2 cm or multifocal, especially if a PMD or carcinoma in situ/OSCC is suspected, an incisional single or multiple biopsy is recommended, eventually preceded by mapping with a vital colorant (Toluidine blue) or a visual device (e.g. VelScope®, Sapphire®). The complete excision of the lesion should be postponed after histological diagnosis and diversified on the basis of the presence and degree of dysplasia or carcinoma. However, the patients should be informed that, in light of the multifocal nature of oral and oropharyngeal infection, surgical removal of the lesion does not guarantee elimination of the infection, because viral DNA could persist in the normal adjacent mucosa [41].

CONCLUSION

HPV infection associated with the head and neck region affects approximately 750,000 patients worldwide every year with the common type being HPV head and neck squamous cell carcinoma (HNSCC), which is considered as a lethal cancer that develops in the epithelial linings of the oral cavity, pharynx and larynx. HNSCC is strongly associated with tobacco smoking and alcohol consumption in the past few years. The role of high-risk human papillomaviruses (HPV) is emerged as an important etiological factor for a subset of HNSCC arising from the oropharynx. The incidence of HPV-driven oropharyngeal SCC (OPSCC) is also known to be dramatically increasing in developed countries predominantly affecting male population, than tobacco and alcohol related carcinomas. And it is supposed to be mainly linked to changes in their sexual behaviours over the past few years. Oral HPV infection is considered as a precursor of HPV-driven OPSCC. But still the natural history of oral HPV infection is not yet entirely understood.

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