Review Article

HUMAN PAPILLOMA VIRUS INFECTION AND ITS ORAL MANIFESTATION

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Abstract

Papilloma viruses, member of papillo-viradae family of virus, are tissue and host specific. Thus, the cross infection between species is rare. Papilloma viruses infect the outer surface of tissue and replicate exclusively in the cells of basal layer of the epithelium. Human papilloma virus (HPV) which is a double stranded DNA (ds DNA) virus has 200 subtypes. These viruses are epitheliotropic and can infect and cause lesions in various epithelial tissues of different anatomic sites such as the skin, anogenital areas and mucosa of upper aerodigestive tract. HPV infection could be asymptomatic and self-limiting, or it can manifest as a simple wart to malignancy. RT-PCR is considered as gold standard method to diagnose HPV presence in any lesion. Recent introduction of novel surgical methods and technique improved the prognosis of the HPV lesions as well as reduced the morbidity and disfigurement which were reported in past. Now HPV vaccines are implemented for prevention of HPV infection.

INTRODUCTION:

One of the most primitive viruses includes Human Papilloma virus (HPV) which started developing around 330 million years back in paleozoic era with. These viruses acquired the ability to harvest complete cellular machinery and protein infrastructure for reproduction and avoid immunity by hijacking cellular and immune system at different levels.[1] HPV believes to be the most common virus infecting humans; in some endemic population it can affect the whole population. Almost every person on the earth is infected by HPV once in a lifetime. HPV is the most common sexually transmitted virus in the world but 90% of HPV infections are asymptomatic and resolves spontaneously within two years.[2] HPVs are transmitted either by direct contact i.e. sexual intercourse or oral contact with the mucous membranes of an infected subject or by indirect contact with infected medical instrument or contaminated utensils. In both the mode of transmission, transportation of virus is facilitated to the basal layer of epithelium through microlesion in the intact surface.[3]

THE HPV GENOME:

The genetic component of HPV is non-enveloped, circular, Double stranded (Ds) DNA genome. HPV has a size of about 8000 base pairs, constituting 8 open reading frames (ORFs).[4, 5] The HPV genome constitutes 3 main segments. **1). The Early Region (E)** – encodes the proteins of virus which are numbers as E1 to E7. E1 region controls the transcription of viral DNA, E5, E6, E7 codes for the oncogenic property of the virus and leads to cellular immune-editing.[6] **2). Late region (L**)- The late region, covering almost 40% of the virus genome and codes for the capsid proteins. **3). A non-coding long control region (LCR**)- it plays a vital role in regulating the viral RNA polymerase-II and initiates transcription from viral promoters.

CLASSIFICATION OF HPV:

Phylogenetically, HPVs are classified into different genera, species and types. In Genera classification HPVs are categorised into alpha, beta, gamma, mu, nu. L1 gene of HPV is most evolutionary conserved gene of HPVs. The sequence analysis of these L1 genes is the basic principle behind the classification of HPV types.[7]

THE HPV LIFE CYCLE

HPV is a tissue-trophic virus and shows selective affinity for keratinocytes. HPV infects the basal cells of squamous epithelium of the different anatomical areas of the body. Micro-lesions in the outer and most superficial surface of epithelium facilitate the entry of virus particle into the basal layer of the epithelium. Viruses infects the basal cells at first then it undergoes viral DNA synthesis and DNA is linked to capsid proteins as the keratinocytes matures and transforms in different epithelial layers. Viruses released from the stratum corneum and granulosum directly infect the basal layer and repeat the cycle.[8]

Once a virus penetrates the basal cell, it replicates by three major mechanisms namely: plasmid, vegetative, and productive replication. Cellular modification from basal layer and upward, provide suitable micro-atmosphere for HPV to replicate and reproduce. **Vegetative stage**: Epithelial cells differentiate from basal cell into keratinocytes, with the cell differentiation viruses inside the basal cell replicate and express the viral genes. **Productive stage: C**ytopathic effects of virus manifest in productive stage, these changes include

acanthosis, dyskeratosis, multinucleation of keratinocytes, and koilocytosis i.e. thickening of peripheral cytoplasm and stellate nucleus. Koilocytosis is considered pathognomic in HPV lesions.

EPIDEMOLOGY

Human Papillomavirus (HPV) infection is one of the most common sexually transmitted infection (STI). Every year 6 million people are diagnosed positive for HPV. About 9 - 13 % of the population of world is infected with HPV [10] whereas oral HPV infection prevalence is approximately 5-10%. The incidence of cervix infection is much higher than the oral infections. HPV positive head and neck squamous cell carcinoma is more prevalent in younger patients (< 50 years) in comparison to typical head and neck malignancies.

HPV's ONCOLOGICAL ACTIVITY:

Oncological activity of HPV is primarily due to E6 and E7 oncoproteins of HPV. As the expression of E6 and E7 genes increases, increase in cellular proliferation is reported. Integration of the viral genome is considered as a critical step in pathogenesis of HPV related cancer. E6 gene target the p53 gene, a tumor suppressor gene, and inhibit it causing decrease in apoptosis and cause cell cycle arrest. E7 gene protein degrade and inactivates pRb, which in turn prevents inhibition of the E2F transcription factor hence leading to loss of cell cycle control. Loss of cell cycle control and inhibition of physiological apoptosis in HPV infected cells leads accumulation of genetic damages and could cause mutation leading to malignant change. [11]

IMMUNE RESPONSE TO HPV

HPV evades both innate and humoral component of immunity in number of ways, as:

1. HPVs avoid antigenic reaction by replicating within the cells without cytolysis, thus avoiding antigenic presentation and hence cellular immune-survellience.[12]
2. HPVs avoid detection of capsid protein by Langerhans cells by limiting expression of their capsid protein to superficial differentiated epithelial cells.
3. HPVs are also known to disturb the function of interferons, E6 & E7 proteins can prevent immunoregulation by interferon-α and β. High risk genotypes could down-regulate INF-α inducible gene expression.[13]
4. E7 gene expression can evade or supress normal immunological response of host.[11]

DIAGNOSTIC TOOLS FOR HPV:

Diagnostic tests for HPV aim for detection of HPV DNA or RNA in tissue samples. These tools are broadly classified as: target amplification method or signal amplification method. **(i) Target Amplification Method**: **Polymerase Chain Reaction (PCR)** is most commonly used method for HPV detection. **Real Time PCR** amplifies HPV sequences and gives a quantitative result and HPV viral load which are clinically important. **(ii) Signal Amplification Methods**: In situ hybridization assay involve the hybridization of nuclei acids from virus with target specific probes and are visualized in-situ. ISH could visualize HPV DNA directly within the nuclei of cells of sample tissue. Low sensitivity and being technique sensitive are the demerits of ISH.[14] **(iii) Viral mRNA Detection**: It is the gold standard test for transcriptionally active HPV infection where frozen tissue is tested for E6 and E7 mRNA. This test has demerits of being very technique sensitive and requires significantly more tissue.[14] **(iv) Immunohistochemical staining for p16:** IHC for p16 protein is used for high risk subtype of HPV. It is cost-effective and reliably applied which is about 100% sensitive but specificity is only 79%. [15]

BENIGN LESIONS CAUSED BY HPV:

Several benign oral lesions are caused by low-risk HPV such as squamous papilloma, condyloma acuminatum, verruca vulgaris etc.

ORAL SQUAMOUS PAPILLOMAS: It occurs commonly in the oral cavity. Clinically, papillomas generally measure 1 cm in size and are pink to white in colour, exophytic or cauliflower-like in appearance. They are generally asymptomatic. OSP are classified into two types: Isolated-solitary are found in adult oral cavity and multiple-recurring in children. Immuno-compromised HIV positive patients often have multiple papillomas at a time.[16]

CONDYLOMA ACCUMINATUM: It is a sexually transferable, proliferative lesion which could affect both genital and oral regions. Subtype 6 and 11 of HPV are most common strains which cause condylomas. Condylomas have warty appearance, but larger in size with blunted surface projections and can coalesce into a larger lesion. When large tumour like mass covers the entire anogenital area then it is known as Buschke-Lowenstein tumor, and it could have malignancy potential. Oral condylomas are commonly present on the tongue and lip. Oral condylomas appear as raised, skin coloured, fleshy papule, which varies in sizes from 1 mm to 5mm.

VERRUCA VULGARIS also known as common warts and are most commonly seen in children. They are exophytic cutaneous lesion and can also be found on mucous membranes. Warts are common and affect approximately 10% of the human population. They are more common among immunosuppressed patients and meat handlers (Butcher's warts). Warts are twice as common in Whites as in Blacks or Asians.[18] **Clinically**, verrucae are either solitary or multiple. They generally appear as small, white and well demarcated

lesions over vermillion borders, labial mucosa and anterior tongue region.[18]

FOCAL EPITHELIAL HYPERPLASIA also known as Heck's disease or multifocal papilloma. It is a rare benign lesion caused by HPV subtypes 13 or 32. 1t can be mostly found in children or young adults. FEH is more frequent in immuno-compromised and in lower socio-economic status. FEH show specificity toward some ethnic population and are seen more frequently in aboriginal population of Native Americans, Eskimos and South African.[19] Genetic predisposition of the disease is explained by familial occurrence of FEH. Clinically, FEH presents as clusters of flat-topped nodules or "cobblestones". It can be characterized by multiple, painless, soft, sessile papules, plaques or nodules, measuring 1 to 10 mm in diameter, lesions may coalesce to give rise to larger lesions. These lesions are painless and tend to disappear spontaneously. Lesions are predominantly found on the lower lip, buccal mucosa and tongue.[19]

HISTOLOGICAL FEATURES: The histopathological examination of these lesions in general reveals stratified squamous hyper-parakeratinized epithelium with multiple papillary projections and a fibrovascular connective tissue core. The epithelium usually has few clear cells in the superficial layer suggestive of "koilocytes". This cell is thought to be indicative of a virally altered state. The surface of the epithelium has few hornlike projections suggestive of "chevron". Few scattered lymphocytes could be present in the stroma of the stalk, body, and projections of the lesion. Chronic inflammatory cells are also common. Histologically, FEH is characterized by fusion and horizontal outgrowth of epithelial ridges, can be denoted as club or battle-axe shaped rete ridges.

TREATMENT: In most of the cases, in a healthy young patient, HPV warts or lesions resolves spontaneously in few months to years. Treatment is needed for lesions which are either symptomatic or which persist for more than 2 years. Surgical excision is the treatment of choice. Podophyllotoxin 0.5% solution and Imiquimod cream 5% are two topical drugs which could be used for treatment of papules. Cryotherapy is inexpensive, minimally painful and is safe during pregnancy.

HPV's ASSOCIATION WITH PREMALIGNANT LESIONS:

Carcinogenetic effect of HPV in premalignant lesion is still doubtful and is a debateable topic. Some researchers believe that HPV could have carcinogenetic effect in premalignant lesions whereas others reported that premalignant lesions which are HPV positive shows better prognosis with respect to HPV negative premalignant lesions. HPV as a cause or contributor in cause of premalignant lesion are completely rejected. Hence it is unclear, whether an analogous relationship exists in the oral cavity or not.[20]

HPV's ASSOCIATION WITH HEAD AND NECK SQUAMOUS CELL CARCINOMA:

HPV infection is evident to play causative role in etiopathogenesis of squamous cell carcinoma on oral as well as anogenital areas. About 20% of oral squamous cell cancers and 60% - 80% of Oro-pharyngeal carcinomas are related to HPV infection. The International Agency of Research of Cancer (IARC) in 2012 declared the association of HPV subtype 16 with oral squamous cell carcinomas. Thus, now it is well established that high risk HPV, in particular subtype 16, plays a causative role in the development of oral squamous cell carcinomas.[21] HPV positive carcinomas shows distinct epidemiologic, molecular and risk factor profile in comparison to HPV negative carcinomas. According to V. Candotto, the risk of HPV infection in oral squamous cell carcinomas is about four times when compared to patients with healthy mucous membranes.[20]

Immunohistochemistry (IHC): HPV positive malignancies show p16 overexpression whereas expression of p53 and bcl-2 is not associated with HPV positive oral squamous cell carcinoma and mutations in p53 are rarely seen in HPV positive cases. Hence, genetic signatures of HPV positive oral squamous cell carcinoma is different from those of HPV negative oral squamous cell carcinoma.[22]

TREATMENT: unlike other viral infections, clinically no drug is available which could eradicate or regress HPV infection. As HPV infection does not respond to any pharmacological therapy, the treatment option left is predominantly surgical. The surgical treatment is the excisional treatment with cold-bladed scalpels, quantum or laser resonance scales, which allows the histological examination of the sample. There is no evidence to indicate that treatment is different from that with other cancers arising in this area.

HPV VACCINE:

HPV vaccines are based on the principle that major capsid antigen L1 of HPV could assemble into virus like particles (VLP) which are devoid of viral DNA. These virus like particles could induce antibody formation hence cause immunity against HPV. At present US FDA approved two cervical cancer vaccines namely, Gardasil, a quadrivalent vaccine and Cervarix, a bivalent vaccine.[23] Gardasil is composed of VLPs from major L1 capsid proteins of subtypes 6,11,16,18 of HPV, hence it is active against these subtypes of HPVs. HPV vaccines are recommended for 11 to 26 years of female and adolescent males in several countries.[24] Around 40 countries have introduced HPV vaccines in their immunisation program. Due to the vaccination drives against

HPV, prevalence of oral HPV infection in middle aged adults has decreased.[25]

CONCLUSION:

HPV is one of the most common viral infection, but general population has a little knowledge about clinical presentation and transmission of HPV infection. Mostly patients sought homeopathic remedies, which could lead to more spread. Hence proper information campaigns, awareness program about its contagious nature and availability of vaccines is the need of the hour.

For clinicians and researchers, as the information about the HPV infection and its carcinogenetic potential has increased considerably and with newer advances in molecular biology techniques, they have new challenges to device better measures of infection control and formulate more definitive therapeutic protocols.

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