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A REVIEW OF HPV-RELATED AND NON HPV- RELATED HEAD AND NECK CANCER

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ABSTRACT

Oral Malignancies are one of the commonest causes for mortality and morbidity with squamous cell carcinoma, as it is the sixth most frequent malignant tumour worldwide. In addition to tobacco and alcohol, human papilloma virus (HPV) is associated with a proportion of head and neck cancers. As in cervical cancers, HPV types 16 and 18 are the cause of malignant transformation. HPV- positive cancers of head and neck have unique characteristics such as occurrence in a younger age group, distinct clinical and molecular features, and better prognosis as compared to HPV- negative carcinomas. They also possess the potential for prevention by using vaccination. The current review depicts in detail the notable highlights of HPV related oral squamous cell carcinoma (OSCC), its disparities from HPV- negative OSCC, indicative highlights, and late techniques in avoidance and the board. In this audit, we will sumup the sub-atomic reason for this distinctive result, novel treatment openings and conceivable biomarkers for HPV positive HNSCC.

KEYWORDS: HPV; HNSCC (Head and Neck Cancer); Radiation Therapy; Molecular Pathogenesis.

INTRODUCTION

Human papillomavirus (HPV)-related carcinogenesis has been attributed to a subset of head and neck cancers.[1] Those cancers includes squamous cell carcinoma of the head and neck (HNSCC), and primarily arise in the oropharynx (OPSCC) and mainly in the tonsils**.** Squamous cell carcinoma (SCC) is the most frequent oral cavity malignancy accounting for over 90% of oral cancers.[2] It is expected that HPV- related HNSCC have unsimilar contributing elements contrasted with HPV- negative HNSCC, e.g., sexual conduct instead of tobacco and liquor consumption. It is defined as "a malignant epithelial neoplasm exhibiting squamous differentiation as characterised by the formation of keratin and/or the presence of intercellular bridges".[2] It contributes the sixth most frequent malignancy worldwide.[2] Human papillomavirus (HPV) is the most common sexually transmitted viral infection.[3] HPV has also been established as the causative agent in cervical cancer.

***Structure of HPV*:** HPV belongs to the family Papilloma viridae and is a small, non- enveloped DNA virus, having diameter of 52–55 nm. The genome consists of double-stranded DNA bound to cellular histones and surrounded by a protein capsid.[3] The eight open reading frames (ORFs) have three functional components: the early (E) region, the late (L) region, and a long control region (LCR). The early region is essential for replication, cellular transformation, and viral transcription; the late region forms structural proteins (L1-L2) essential for virion assembly; and the long control region is necessary for the replication and transcription of viral DNA.[3] The early (E) region of the ORF encodes seven proteins: E1 to E7. E1 is necessary for viral DNA replication. E2 has a role in viral gene Transcription and replication[3] E6 induces DNA synthesis, prevents cell differentiation, interacts with tumour suppressor proteins and repair factors; and E7 induces cell proliferation and interacts with negative regulators of cell cycle and tumour suppressor proteins. E6 and E7 proteins act as oncogenes which are causally associated with carcinogenesis.

History

Zur Hausen, in the 1970s, proposed that cervical cancer and condylomata acuminate may have a common viral etiology, that is, HPV 6–8.[4] Syrjanen in 1983 first suggested HPV as a causative agent of head and neck cancer due to the same clinical features in oral and genital injuries as well as similarities in the epithelia, affinity of HPV for epithelial cells, and its oncogenic potential.[2]

Epidemiology

A systematic review of HPV associated head and neck

squamous cell carcinoma (HNSCC) found a prevalence of 25.9%.The prevalence was higher in oropharyngeal squamous cell carcinoma (OPSCC) (35.6%) compared to oral (23.5%) and laryngeal (24.0%) SCC.[2] Kulkarni et al.[7] in a study conducted in Karnataka, India, found that 96% of cervical cancer was positive for HPV, 70.59% was positive in OSCC, and 84% in general population. Their results showed higher HPV 18 prevalence as compared to HPV16 in general population.

Risk Factors

Oropharyngeal cancers associated with HPV have contributory factors such as more number of sexual partners, oral-genital sex, and oral-anal sex. Marijuana use is an independent risk factor for HPV-positive HNSCC, and the risk increases with the intensity, duration, and cumulative years of marijuana smoking.[2] Herrero et al.[8] found that HPV is detected less frequently in ex-smokers, current smokers, and tobacco chewers as compared to non-smokers and no chewers. HPV detection is also more frequent in subjects with greater than one lifetime sexual partner and in subjects with history of oral sex. The relationship of HPV DNA with sexual behaviour was similar for both oral and oropharyngeal cancers.[8]

Etiopathogenesis

HPV induced HNSCC

The oncogenic potential of HPV is because of its ability to incorporate E6 and E7 into the hostgenome leading to inactivation of the tumour suppressor genes p53 and p16.[2] E6 protein ofHPV can affect p53 in the following two ways: it can bind to it causing its degradation or it can inhibit p300 mediated p53 acetylation, which affects its function. The carcinogenic effect of alcohol, tobacco, and other related carcinogens may be increased by HPV infection. Defective apoptosis, neovascularisation, and cellular immortality are also prevalently related with HPV infection. Thus, HPV mediated carcinogenesis may be an integrated process due to the result of various contributory factors.[2]

Transmission of HPV infection

HPVs are prevalent worldwide and infection with cutaneous HPV is ubiquitous.[7] The common mode of transmission and acquisition of HPV is by horizontal transmission consequent to sexual activity.[3] Occasionally, HPV may be transmitted through modes other than sexual activity. These routes include vertical transmission (mother to child), fomites and skin contact.[3]

Pathology of HPV infection

HPV infections can cause a range of pathological lesions of the female cervix, male and female ano-genital tract, upper respiratory tract, oral cavity and conjunctiva.[3]

HNSCC (non HPV induced) – It develops mostly via one of the two primary carcinogenic routes, namely the chemical carcinogenesis through exposure to tobacco and alcohol abuse, which are known to be synergistic.[5]

Clinical Aspects

HPV-positive oral cancer occurs in younger age group as compared to HPV-negative cancers with an average age difference of 4–10 years. HPV-positive patients also have higher income and more years of education.[2] The male: female ratio is 5:1.[2]

	HPV Positive	HPV Negative
Clinical, epidemiological characteristics		
Incidence	Increasing	Decreasing
Age	Younger	Older
Socioeconomic status	Higher	Lower
Risk factors	Sexual behavior, marijuana exposure	Tobacco and alcohol exposure
Location of the tumor	Oropharynx (common in tonsil and BOT)	All head and neck sites (common in floor of mouth, lateral tongue and ventral tongue)
Prognosis	good	poor
Biological and histopathology characteristics		
TP53 pathway	E6 mediated degradation	TP53 mutations
RB pathway	E7 mediated degradation	Inactivating mutations or other alterations in pathway
p16INK4a expression	Commonly overexpressed	Commonly decreased expression (inactivating mutations and hyper methylation)
Histology	Poorly differentiated or basaloid SCC	Modestly to well differentiated, keratinized SCC

Abbreviations: HPV, Human papillomavirus; BOT, Base of tongue; SCC, squamous cell carcinoma. [5]

Diagnosis

The common methods being used in diagnosis of HPV are viral DNA detection with polymerase chain reaction (PCR) or In Situ Hybridization and p16 detection by immunohistochemistry. Amplification of target DNA sequences by PCR followed by hybridization with dedicated probes is the commonest method for HPV detection and genotyping.[2] Studies have suggested that p16 positivity can be used as a biomarker for HPV associated tumours and also as a prognostic factor in HNSCC. Antibodies to HPV can be detected in the serum and is a measure of the cumulative exposure of an individual to HPV infection.[2]

Histopathology

The pathologic features of HPV-positive tumours are different from HPV-negative tumours inthe following:

(a) They are not related with surface dysplasia or keratinisation.
(b) They exhibit lobular growth.
(c) They have infiltrating lymphocytes.
(d) Basaloid variants are common.

HPV-positive tumours are usually well differentiated and the basaloid tumours have goodprognosis.[2]

Treatment Response

HNSCC treatment is based on combination of three major treatment arms, namely surgery, Chemotherapy and radiotherapy (RT).[5] For metastasized disease, generally systemic treatment like chemotherapy is preferred. However, in locally advanced disease, surgery and RT play an important role, with or without chemotherapy. Interestingly, several retrospective and prospective trials have shown that HPV+ HNSCC patients have better overall survival, disease free survival (DFS) and loco-regional control (LRC) compared to the HPV- patients and this is independent of the treatment modality. In general the 5-year overall survival for HPV-HNSCC is around 50% while for HPV+ HNSCC patients values around 80% can be reached.[5]

Prognosis

Oral squamous cell carcinoma has significant mortality and morbidity rates despite the enormous. Cessation of smoking and alcohol habits has a favourable prognosis on OSCC and fruits and vegetables have a protective effect especially citrus fruits, fresh tomatoes, green peppers, and carrots[2] Rich vascular and lymphatic network, local extension, stage of the tumour at presentation, and cervical node metastasis are associated with poor prognosis. Among the molecular markers, aberrations in chromosomes 3, 9, 11, 13, and 17 and tumour suppressor genes like p53 and pRb are implicated.

Vaccination

One of the methods proposed for prevention of HPV related oropharyngeal cancer (OPC) is vaccination. At present, there are two vaccines available: the HPV 16/18 vaccine Cervarix and the HPV 6/11/16/18 vaccine Gardasil.[2] Recommended HPV vaccination for females and males between the ages of 11 and 12 years, as early as 9 years, and booster doses up to 26 and 21 years for females and males, respectively.[2] HPV-positive cells are believed to be more sensitive to radiation as compared to HPV-negative cells.[3]

CONCLUSION

HPV-positive head and neck cancers thus differ from HPV-negative tumours in epidemiology, clinical features, molecular profile, and response to therapy.

SUMMARY

Human Papilloma Virus associated oral and oropharyngeal head and neck carcinomas have features which are distinct from the tobacco and alcohol related squamous cell carcinomas.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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