

HEAD AND NECK SQUAMOUS CELL CARCINOMA

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REVIEW

World-wide the head and neck squamous cell carcinoma is (HNSCC) sixth most common cancer.¹ HNSCC is most common cancer in developing countries.² While HNSCC form one of the most common cancer in South and Southeast Asian countries, they form only 1 – 4 % of all cancers in the western world.³ Oral cancers are predominant forms of HNSCC in India, Pakistan and other South-Asian countries, oropharyngeal and tongue cancers are common in the western world. These observations are compatible with the study done at our Histopathology department Liaquat National Hospital. The most common location of HNSCC was the oral cavity.⁵ These differences in the site of disease may be related to prevalent habits in the respective regions.

Oral cancer / HNSCC is a serious problem in Karachi. Most of these are due to preventable risk factors. These risk factors are mostly found to be smokeless chewable Tobacco products with added dried areca nuts. These products include gutka, naswar, paan etc. The two published studies, conducted in Karachi's population^{5,6}, suggested gutka as the most common form of consumption of chewable tobacco. We are conducting a retrospective study at our patients of LNH to evaluate histopathological correlation between smoker and smokeless tobacco in patients with oral cancers. We have observed that the use of smokeless tobacco had higher risk of causing carcinoma of the lip, cheek and tongue as compared to smoked tobacco (OR 2.5 vs 0.78). These are the most common sites affected in oral cavity in South – Asian population. Our

results also indicate that smokeless tobacco causes more harm in the oral region as compared to smoked tobacco in terms of cause, tumour grade and lymph node metastasis. This is probably the causes of high morbidity and mortality found in our patients of HNSCC. Definitely, further studies are warranted in this aspect. This data was presented at histopathology and cytopathology conference at Lahore in 2015. This is yet in the process of publication.

The link between HNSCC and HPV has become established. Evidence for a mutational progression in tumorigenesis of head and neck squamous cell carcinoma (HNSCC) first derived from cytogenetic studies that demonstrated nonrandom clonal losses, duplications, and rearrangements of chromosome segments in head and neck tumours⁷. Within many of these regions of recurring chromosomal abnormality, candidate oncogenes or tumour suppressors have since been identified, some of which appear to play critical roles in carcinogenic transformation⁸. Identification of some of the critical genetic events leading to head and neck cancer has clarified the molecular basis for epidemiologic observations regarding risk factors (e.g., tobacco), identified previously unknown risk factors (e.g., human papillomavirus infection), and is yielding information that may be critical for risk stratification.

HPVs are DNA viruses that show a tropism for squamous epithelium. HPV is a strictly epitheliotropic, circular double-stranded DNA virus. There are more than 100 subtypes of HPV, some of which are involved in and have been designated as high-risk HPVs (e.g. HPV-16 and -18). HPV-positive HNSCCs present with distinct molecular profiles compared to HPV-negative tumours whereas they harbor similarities with HPV-positive cervical SCCs. Most HPV-induced HNSCCs are caused by one subtype, HPV-16. HPV infection is an early, and probably initiating, oncogenic event in HNSCCs. High-risk oncogenic HPV subtypes have been shown to be capable of transforming oral epithelial

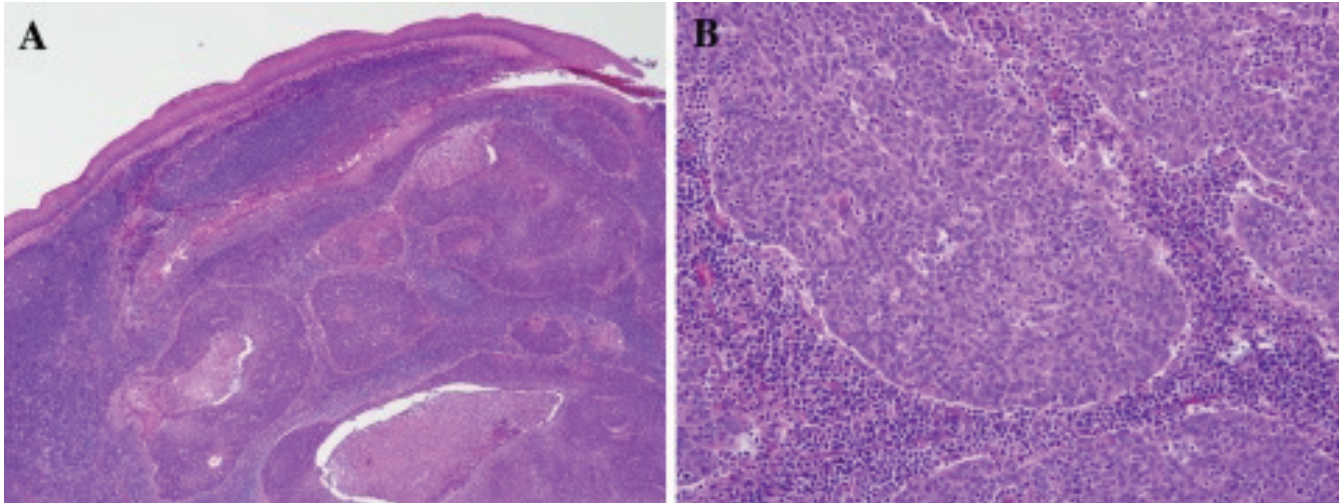


Fig.1. (a) HNSCC Consistently arise from tonsillar crypts

(b) Basaloid morphology

cells through the viral oncoproteins E6 and E7. The E6 protein induces degradation of p53 through ubiquitin-mediated proteolysis, leading to substantial loss of p53 activity. The usual function of p53 is to arrest cells in G1 or induce apoptosis to allow host DNA to be repaired. E6-expressing cells are not capable of this p53-mediated response to DNA damage and, hence, are susceptible to genomic instability. The E7 protein binds and inactivates the retinoblastoma tumour suppressor gene product pRB, causing the cell to enter S-phase, leading to cell cycle disruption. This functional inactivation of pRB also results in a reciprocal over expression of p16 protein. By immunohistochemistry, most HPV-positive HNSCCs show p16 overexpression⁹. The combination of low EGFR and high p16 expression has been shown to highly correlate with better clinical outcome compared with high EGFR expression and low HPV titer or high EGFR and low p16 expression. P16 expression in oropharyngeal SCCs has also been associated with longer survival times regardless of HPV status¹⁰.

The human papilloma virus (HPV) is now a recognized causative agent for a subset of carcinomas arising from mucosal lining of the head and neck. A better understanding of the role of HPV as a cancer causing agent tumours may provide new ways to effectively prevent and treat HPV related cancers of Head & Neck. Clearly, accurate detection of HPV in the cancer samples will be necessary to determine which patients will most likely benefit from HPV related therapy.

HPV, particularly type 16, is detected in about 70% of Oropharyngeal carcinoma. The HPV – positive cancers

are increasing by recognized as a distinct subgroup of HNSCC with a biological and clinical profile that diverges from that of their HPV negative counterparts. At molecular genetic level, HPV positive HNSCC express, the viral Oncoprotein E6 and E7, over express the p16 gene product, and only infrequently harbor p53 gene mutations.

The pathologic features of HPV – positive HNSCC also deviate from moderately differentiated keratinizing morphology that typifies most HNSCCs¹¹. HPV positive HNSCCs consistently arise from

- Tonsillar crypts (fig 1.a),
- Unassociated with dysplasia of the surface epithelium,
- Exhibit lobular growth,
- Infiltrating lymphocytes,
- Lack significant keratinization and
- Demonstrate “basaloid” morphology (fig 1.b).

Determination of HPV status will certainly become standard practice in the pathologic evaluation of Oropharyngeal cancers. A variety of detection method are in current use including PCR – based strategies, type – specific insitu hybridization (ISH) techniques, and IHC detection of surrogate biomarkers.

Now a days most widely used and considered reliable test is detection of HPV-16, the most common HPV subtype to cause cancers of head and neck. This is highly sensitive and applicable to formalin – fixed

paraffin embedded clinical samples and permits direct visualization of viral sequences within tissues.

As discussed earlier, several epidemiological studies have established and proved relationship between HNSCC and HPV. Now what is important in our culture / city is that if the oral mucosa has exposure to both HPV and chewable tobacco, is there increased risk of oral HNSCC ?. This may be responsible for increase risk of HNSCC in Pakistan which has been raised to 8.5 to 10 times in the recent years.

It has been observed that epithelia areas of upper aero-digestive tract display great susceptibility to HPV due to easy exposure of basal cells to HPV infections. Our observation is that HPV transmission in oral squamous mucosal cells is facilitated by variety of habitual and culturally based activities of chewing tobacco with worst out comes with gutka, which is the most common in Karachi, as also shown by our study.

One of the studies conducted by department of Biochemistry, Ziauddin University⁶ showed that usage of chewable tobacco formulation is associated with high frequency of HPV infection. OR = 7.981 (CI 4.587-13.89). The reasons most likely are that oral mucosa of chronic users of chewable tobacco is constantly eroded results in abrasions, ulcers and make it susceptible to HPV and virus gains entry easily into basal layer of squamous epithelium.

In conclusions, as HNSCC particularly oral squamous cell carcinoma is largely due to preventable risk factors (chewable tobacco) in our setup. These are easily available cheap and widely consumed, despite having serious health risks posed by them. Therefore, efforts of early detection of oral cancer and public awareness should be made to overcome this epidemic of oral cancer.

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