Human Papillomavirus (HPV) Related Carcinomas of the Upper Aerodigestive Tract

Samir K. El-Mofty

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Abstract Epidemiologic, clinical, morphologic and molecular evidence show that high risk HPV, particularly type 16, is a prerequisite for some carcinomas of the upper aerodigestive tract (UADT), particularly tonsil and base of tongue. Sexual transmission is an important mode of infection while tobacco use and excessive drinking are not considered risk factors. HPV + tumors are distinct clinically and pathologically. They are more common in young patients (<40 years) with a male to female ratio of 4:1. They usually present as a small or occult primary tumor with advanced neck disease. Microscopically they are non-keratinizing squamous cell carcinomas with basaloid features, excessive mitosis and comedo type necrosis. The tumors have a distinct immunohistochemical profile characterized by strong and diffuse p16 reactivity, low or negative p53 staining and high Ki67 labeling scores. HPV + carcinomas are more radio-sensitive and have a better prognosis than the classical keratinizing SCC of the UADT. An anti-HPV vaccine has recently been made available for prevention of cervical cancer. The impact of the vaccine on the prevalence of HPV related carcinomas of the UADT is currently not known but likely beneficial.

Keywords Human papillomavirus · HPV16 · Upper aerodigestive tract · Oropharynx · Tonsils · Base of tongue · Non-keratinizing squamous cell carcinoma · p16 · Sexual transmission · Radiosensitivity · Vaccine

Background

The role of human Papillomavirus (HPV) as a prerequisite for the development of cancer of the uterine cervix has been established for many years. The prevalence of high risk (oncogenic) HPV infection in cervical cancer tissue is estimated to be in the range of 90–99%. According to the WHO, about 500,000 new cases of cervical cancer occur globally each year. The majority is identified in developing countries [1–3]. According to CDC epidemiologic studies, 75% of the 15–75 year-old population in the United States acquire genital HPV infection at some point in their lives. By the age of 50 at least 80% of women will have acquired genital HPV infection [1–4].

More recently epidemiologic, clinical and molecular evidence have implicated HPV particularly type 16 in the causation of some upper aerodigestive tract (UADT) carcinomas, particularly in the oropharynx and notably the tonsils and base of tongue [5–14].

The Virus

Human papillomaviruses belong to the family of DNA Papovaviridae. They are small non-enveloped icosahedral viruses with an 8 Kb-long double-stranded circular DNA genome. They include more than a 100 different strains or genotypes, more than 30 of which are sexually transmitted, infecting the genital areas of men and women. Some of these viruses can cause premalignant lesions and carcinomas in the affected areas, and are called “high-risk” types. Others called “low-risk” types may cause mild cytologic abnormalities and genital warts as well as laryngeal papillomatosis and oral condyloma acuminata. The most common high-risk types are types 16 and 18,

S. K. El-Mofty (✉)
Washington University, St Louis, MO, USA
e-mail: elmofty@wustl.edu

while the most common of the low risk ones are types 6 and 11.

Human papillomavirus genome is made up of 7 early (E) genes and 2 late (L) genes that encode the early proteins E1–E7 and late proteins L1–L2 respectively (Fig. 1). The E proteins are nonstructural and are involved in replication and transcription of the genome, while the L proteins are the structural capsid proteins of the intact virion [15, 16, 3]. Molecular evidence in cervical as well as oropharyngeal carcinomas show that the HPV oncogenes E6 and E7 act through inactivation of p53 and retinoblastoma (Rb) tumor suppressor genes, respectively, inducing cell cycle deregulation and genomic instability. In addition E6 can directly activate telomerase and E7 induces abnormal centrosome duplication [3, 15, 16].

HPV-related Carcinomas of the Head and Neck

During the last few decades there has been an increase in incidence of oropharyngeal carcinoma in young patients under 45 years of age. Using the SEER data base a statistically significant increase in incidence of carcinomas of the tonsils and base of tongue was documented during the period 1973–2001 in the US population aged 20–44 years. No similar increase occurred in other oral sites outside the oropharynx. Many of these patients have little or no exposure to known risk factors such as smoking or excessive drinking [17, 18].

About 20 years ago high risk HPV was identified in squamous cell carcinoma of the head and neck [11]. A

multitude of studies using a variety of techniques including in situ hybridization (ISH), immunohistochemistry, and polymerase chain reaction (PCR) have since been able to demonstrate the presence of HPV genome in UADT carcinomas, not only in the oropharynx but also in some laryngeal and sinonasal carcinomas. The virus is very rarely identified in squamous cell carcinoma of the anterior oral cavity [5–14].

HPV-Related Oropharyngeal Squamous Cell Carcinoma

Demographic and Clinical Features

The prevalence of HPV DNA in oropharyngeal carcinoma has varied in different studies from 18 to 90% (6–9, 12, 13). In a review of 235 cases of oropharyngeal carcinomas, in all age groups, at our institution we found that 36% of tonsillar and 32% of base of tongue carcinomas were HPV related [7]. Alternatively, 91% of tonsillar carcinomas in young patients, 40 years of age or younger were HPV type 16 positive [6]. The male to female ratio for all age groups was 4:1 [6, 7].

In another large study of 1,670 patients who had oral or oropharyngeal carcinomas and 1,732 healthy volunteers, from nine countries, the International Agency for Cancer found that 18.3% of oropharyngeal carcinomas were HPV 16 positive. Patients with HPV positive tumors were three times as likely to report having had oral sex as those with HPV negative tumors and were also more likely to have had multiple sex partners [19]. An analysis of the Swedish cancer registry data (1958–1996) showed that husbands of women with cervical cancer had significantly increased risk of developing tonsillar carcinoma [20]. HPV is less frequently detected in cancer biopsies from patients who are tobacco smokers or paan chewers [17–19].

Early asymptomatic carcinomas usually develop in the crypts of the palatine and lingual tonsils without apparent clinical manifestations. Because of their deep location neither clinical examination nor cytologic tests, analogous to the Pap smears used for cervical lesions, are useful in early detection. These small, occult tumors are not uncommonly associated with extensive cervical lymph node metastasis [21]. In the more advanced primary tumors, patients may complain of sore throat, dysphagia, otalgia, and sensation of a foreign body in the throat.

Pathologic Features

HPV-related oropharyngeal carcinomas are not only distinct clinically but also microscopically and molecularly.

Fig. 1 Diagrammatic illustration of Human papilloma virus type 16 genome; E, early genes; L, late genes; LCR, long control region

The tumors are characterized by non-keratinizing, basaloid cell morphology. Microscopically the neoplastic cells are generally monomorphic, oval or spindle shaped, with hyperchromatic basophilic nuclei, inconspicuous cytoplasm and indistinct cell borders. They form cords, sheets and nests with sharply defined borders. Palisading of the peripheral cells may be present. Excessive mitosis and apoptosis are observed as well as comedo type necrosis (6,7) (Fig. 2). Keratinization and keratin pearl formation are generally absent although some trend towards cell maturation may occasionally be present in focal areas (21).

In lymph node metastasis tumor masses commonly show extensive central necrosis leading to a characteristic cystic change (Fig. 3). The lining epithelium of the cystic structures can be so scant and bland appearing that

diagnosis of a benign cyst may be erroneously made, particularly in cases in which the primary tumors are occult.

Immunohistochemistry

A characteristic and distinct immunophenotype is exhibited by oropharyngeal HPV-related non-keratinizing carcinoma. These tumors are distinguished by a strong and diffuse staining for p16INK4a (p16) antibodies (Fig. 4), a negative or weak reactivity to p53 protein and higher Ki67 staining scores (Fig. 5), as compared to the keratinizing type carcinomas of the same site [6, 7, 22]. This immunohistochemical profile is analogous to that seen in HPV positive anogenital carcinomas [23–25].

Fig. 2 HPV related tonsillar non-keratinizing carcinoma with basaloid cell features. Note comedo type necrosis and marked mitosis and apoptosis

Fig. 4 Strong and diffuse reactivity to p16 antibodies in HPV related non-keratinizing carcinoma

Fig. 3 Cystic changes in cervical lymph node metastasis of HPV + non-keratinizing carcinoma

Fig. 5 High labeling score to Ki67 immunostain in non-keratinizing HPV + carcinoma

Detection

As mentioned above the majority of oropharyngeal HPV-related lesions start at the bottom of the crypts of the palatine and lingual tonsils, and thus are inaccessible to routine cytologic smears. Advanced disease is symptomatic and manifest, clinically and radiographically, as a tumor mass usually with enlarged neck lymph nodes.

Occult Primary Tumors

Not uncommonly small primary tumors, which are undetectable on routine clinical or radiographic examination, are associated with significant neck node metastasis [21]. We have recently shown that more than 90% of HPV positive neck metastasis arise from the oropharynx, mainly the tonsils and base of tongue, while less than 10% of those metastasis originated outside the oropharynx including the oral cavity proper, larynx and hypopharynx. HPV related metastatic carcinomas were identified in FNA biopsies as well as in surgical specimens, by morphologic criteria, p16 reactivity and by ISH for high risk HPV [21, 26, 27].

Treatment and Prognosis

An accumulating body of evidence in the American as well as the international literature confirms that HPV positive carcinomas of the tonsils and base of tongue have a statistically significant better prognosis regarding disease free and overall survival than HPV negative tumors. The favorable outcome for patients with HPV positive tumors is independent of TNM stage, nodal status, age or gender [28–33]. It is suggested that the favorable outcome is attributable to higher sensitivity toward radiotherapy.

Prevention

Because HPV infection of the oropharynx is believed to be sexually transmitted, the practice of protective sexual behavior is likely to have preventive effects. Abstinence, monogamy, and limiting the number of sexual partners have all been advocated for prevention of STD. Unfortunately HPV infection can occur in the genital areas that are covered as well as areas not covered by a latex condom. According to NCI the efficacy of the use of condoms in prevention of HPV infection is not known, although condom use has been associated with a lower rate of cervical cancer.

The HPV Vaccine

In June 8, 2006, the Food and Drug Administration (FDA) licensed the first anti HPV vaccine. The quadrivalent vaccine, *Gardasil*, immunizes against HPV types 6, 11, 16 and 18. It is made from non-infectious viral-like particles (VLP) [34–37].

On June 29, 2006, the Advisory Committee on Immunization Practice (ACIP) voted to recommend this vaccine for females, ages 9–26. The vaccine has been tested in over 11,000 females of that age group in many countries around the world including the USA. These studies demonstrated 100% efficacy in preventing cervical precancers, and nearly 100% efficacy in preventing vulvar and vaginal precancers, as well as genital warts, caused by the targeted HPV types. These studies also found that the vaccine is safe and is without side effects [35–37].

The impact of wide use of anti HPV vaccines on HPV-related oropharyngeal carcinoma is currently not known. However it is reasonable to conclude that a direct or indirect benefit may be achieved.

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