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Review article

Human papillomavirus and carcinoma of the mucosal surfaces of the head and neck

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ABSTRACT

Human papillomavirus induced cervical cancer is the fourth most prevalent malignancy affecting females globally. Over the past two decades scientific information unveiled an increasing role for the virus in the pathogenesis of malignancies developing from the mucosal surfaces of the oropharynx. It is feasible to postulate that we may be in the beginning of a global pandemic of oropharyngeal cancer if the mode of transmission of the virus is taken into account. The main goals of this manuscript are to present a brief summary of the mechanisms of human papillomavirus induced malignant transformation, provide guidelines for the microscopic diagnosis of high risk human papillomavirus involvement in mucosal biopsies and highlight the implications thereof in cancers of the mucosal surfaces of the head and neck.

Contents

1. Introduction

Human papillomavirus (HPV) infection is the most prevalent sexually transmitted disease in the world. Oncogenic strains of the virus are directly linked to malignant transformation of the squamo-columnar junction of the female cervix. Cervical cancer caused by HPV is almost three times more common than female breast cancer in developing countries and has a mortality rate of nearly 60% [1]. HPV spreads to the mucosal surfaces of the head and neck through open mouth kissing and/or oral sexual activity [2]. More than 200 HPV types have been recorded. Non-oncogenic varieties with an affinity for the mucosal surfaces of the head and neck include HPV 2, 4, 6, 11, 13 and 32 and cause benign proliferations such as verruca vulgaris, condyloma acuminatum, focal epithelial hyperplasia and recurrent laryngeal papillomatosis (for a review of the non-oncogenic HPV associated mucosal lesions readers are referred to Bharty et al. [3]). Although HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 are classified as high risk oncogenic genotypes for transforming epithelial cells into cancer, HPV type 16 is associated with most malignancies in the head and neck region in which the virus is implicated [3,4]. HPV type 18, which has an affinity for glandular tissue and other oncogenic HPV

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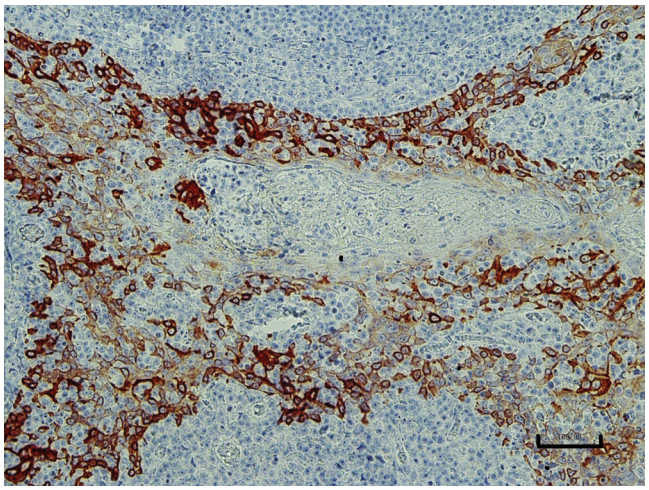

Fig. 1. Loose reticulated epithelial lining of a crypt of a tonsil highlighted by an immunoperoxidase stain for cytokeratin (bar 100 μm).

types are rarely involved in mucosal malignancies in the head and neck region [5].

With 273 000 deaths and 482 000 new cases reported worldwide in 2008, oral and pharyngeal cancer has become the sixth most frequent malignancy affecting mankind [6]. Recent epidemiological studies showed that despite a decrease in the use of tobacco, there is a progressive increase in the incidence of head and neck cancer experienced globally [7]. This trend is attributed to the escalating prevalence of oncogenic HPV infections of the mucosal surfaces of the oropharynx [8]. Studies in North America and Europe claim a 70–80% association between cancer of the oropharynx and HPV [8–10]. World-wide trends in the incidence of oropharyngeal cancer in men between 1983 and 2002 showed a rise in developed countries and a shift towards involvement of a younger age group [11]. This is particularly evident in communities where the traditional risk factors of tobacco and alcohol consumption are on the decline. Changing sexual practices play a defining role in the unfolding of the oral- and pharyngeal oncogenic HPV epidemic. Patients with HPV associated anogenital cancer, which is more common in male homosexuals, have a higher risk for HPV-associated tonsillar cancer than for non-HPV tobacco associated oral cancers [12].

It is feasible to postulate that developing countries with their burden of sexually transmitted diseases, could be on the forefront of the unfolding global epidemic of HPV associated oropharyngeal cancers. The main goals of this manuscript are to provide health care practitioners with an overview of the mechanisms of HPV associated malignant transformation and highlight the importance of determining the involvement of high risk HPV types in lesions affecting the mucosal surfaces of the head and neck.

2. HPV-induced malignant transformation

A requirement for infection of an epithelial cell by HPV is binding of the virus to receptors in the epithelial basement membrane [13]. Most of the oral cavity, oropharynx and larynx are lined by stratified squamous epithelium with tight junctions that provide adequate protection against contact between HPV and the basement membrane. Mucosal ulcerations which are common in the oropharynx and areas in which the epithelium show a functional adaptation towards a loose arrangement such as the reticulated epithelial lining of the oropharyngeal- and lingual tonsillar crypts (Fig. 1), expose the basement membrane binding sites thereby facilitating viral entry into the basally located epithelial stem cells [14]. The ease of access to the basement membrane also apply to the squamo-columnar epithelial junction of the female cervix, which is the site of entry of HPV for the induction of cervical carcinoma. After the virus transfers from the basement membrane to the epithelial cell, it integrates into the nucleus, replicates and propagates in the daughter cells. Natural clearance of HPV occurs in most infected individuals within 2 years, although in some the clearance of HPV 16 takes nearly two times longer [3]. Those individuals in whom HPV type 16 persist, are subjected to a high incidence of malignant transformation.

Due to the malignant potential of HPV 16, its influences on cell reactions have been studied extensively. The success of epithelial infection by HPV 16 is promoted by its ability to evade immune recognition. This occurs through a suspension of E-cadherin dependant Langerhans cell adhesion to epithelial cell surfaces [15], inhibition of Langerhans cell migration to the epithelium [16] and suppression of the release of pro-inflammatory cytokines by epithelial cells which harbour the virus [13].

High risk HPV oncoproteins E6 and E7 play a pivotal role in malignant transformation of infected epithelial cells. These oncoproteins bind to- and inactivate p53 and the retinoblastoma protein (pRB) respectively [17]. During a normal mitotic cycle of an uninfected cell, p53 prevents neoplastic transformation through activation of DNA repair and blockage of cell division by arresting the process in the G1/S phase. When DNA damage is extensive, p53 initiates epithelial cell apoptosis thereby preventing the likelihood of mutations during DNA repair. In an uninfected cell, cycline dependant kinase 4 (CDK 4)-mediated phosphorylation of pRb is a requirement for induction of the mitotic cycle. P16, a tumour suppressor gene, inhibits CDK4-mediated phosphorylation thereby restraining cell division. HPV E7 binds to- and destabilizes pRB [18], the negative feedback of free pRB is subsequently reduced and p16 becomes over-expressed within the infected cell. P16 expression by epithelial cells therefore signals the incorporation of high risk HPVwhich implies that malignant transformation is likely to follow if viral clearance does not occur [17,19].

Epidemiological studies indicate that the incidence of carcinomas of the mucosal surfaces of the head and neck is higher in HIV positive individuals. Although modified tobacco- related habits may play a role in initiating mucosal malignancies in this patient cohort, there is overwhelming evidence that oropharyngeal cancer in HIV positive patients is a consequence of concomitant HPV and HIV infection [17]. Although speculative, the higher rate of infection with HPV of the HIV positive individual is likely the result of a modified lifestyle, altered systemic immune response, breakdown of the innate mucosal immune barriers and suppression of the mucosa-associated adaptive immune response. The impact of HAART on HPV infection and the development of oral and pharyngeal cancer are not yet clarified.

3. HPV identification in biopsy samples

During light microscopic examination of a biopsy or a cervical smear, koilocytes and apoptotic keratinocytes are generally regarded as the hallmark for both oncogenic- and non oncogenic HPV infection (Fig. 2). The appearance of HPV core gene E4, which prepares the cell for the release of viral particles through mediation of enzymatic fragmentation of keratin filaments within the cytoplasm of the infected cell [13], coincides with the onset of koilocytic vacuolation. As E4 expression intensifies, koilocytic vacuolation increases in prominence and cell proliferation declines. The pathognomonic vacuolation is probably a sequel to the cytoplasmic osmotic change resulting from the fragmentation of the filamentous cytokeratin proteins. In oncogenic HPV infection, p16 expression increases in intensity with progressive koilocytic change [20,21]. The morphological identification of koilocytes in

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