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Mini Review

Relation between HPV Infection and the Pathogenesis of the Extra Anogenital Squamous Cell Carcinomas in HIV Positive and Negative Patients

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Abstract

The most extensive and well demonstrated evidence about the association between Human Papillomavirus (HPV) oncogenic type's infection and neoplasm's include the cervical and the anal squamous cell carcinomas. However, the more recent evidence suggested that HPV is involved in the pathogenic of malignancies located at many different sites. The incidence of head and neck cancers, especially those which involve the orpharyngeal anatomic region has actually been increasing. HIV co-infection appears to be as an additional risk factor to develop premalignant and invasive carcinomas of the head and neck, including esophageal Squamous Cell Carcinomas (SCC). In all these cases, HPV demonstrates a specific tropism for cutaneous and mucosal epithelia. In consequence, in all regions with squamous cell epithelium, we can found neoplasm's related with HPV chronic infection. Oncogenic HPV types, especially 16 and 18, appear to target the basal cells of squamous epithelium and increase the risk to develop dysplastic lesions and, eventually, premalignant and malignant lesions. One of the most important risk factor for HPV infection, especially, in men who have sex with men, appears to be HIV co-infection. There is a high prevalence of HPV in HIV positive men; this is especially important in the anal region but it is beginning to be important in warts lesions located in the oral cavity, oropharynx, hipopharynx, larynx and oesophageus. Patients with HPV-oropharyngeal SCC generally have a better response to chemotherapy and radiotherapy in comparison with those with HPV negative tumors.

Keywords: Human Papillomavirus; Human Immunodeficiency Virus; Squamous Cell Carcinomas; Head and Neck

Introduction

The widespread use of highly active antiretroviral therapy (HAART) since 1996 has reduce dramatically the incidence of opportunistic infections and certain AIDS-defining neoplasm's in Human Immunodeficiency Virus (HIV) seropositive patients [1]. The incidence of Kaposi's sarcoma and certain subtypes of Non-Hodgkin's lymphomas (especially primary central nervous system lymphoma) declined 70% [2]. However, HIV-infected people also have an increased risk of non-AIDS defining cancers including those associated with previous viral co-infections as anal cancer related with human papillomavirus (HPV) infection, liver cancer associated with hepatitis B and C viruses and Hodgkin´s lymphoma associated with Epstein-Barr virus infection. Also, lung cancer shows a high incidence in the HIV/AIDS population, related with the high incidence of cigarette smoking [3,4]. The high incidence of these neoplasms is independent of the widespread use of HAART and the immune reconstitution.

Human Papillomavirus (HPV) is the etiologic agent of the most common sexually transmitted infection, named as genital warts or condylomata [5]. There are more than 130 HPV types; some of them are classified as of high-risk according with the potential oncogenic role related with persistent infection [6].

The association between HPV and anogenital cancers has been well described; HPV is responsible for more than 95% of cervical cancers; 85% of anal intraepithelial squamous cell carcinoma (SCC); 65% of vaginal; 50% of vulvar and 35% of penile carcinomas. Additionally, HPV is related with the pathogenic of 45% to 90% of oropharyngeal SCC [7,8]. Generally these malignancies appear after a long period of HIV infection; previous studies showed that HAART has not reduced the prevalence of HPV infection and has not declined the incidence of high grade anal or cervical squamous epithelial lesions [9].

Pathogenic of Squamous Cell Carcinomas of the Head and Neck

Natural history of oral HPV infection include the transformation of normal epithelium of the oropharynx to high grade dysplasia, in situ carcinoma and, finally, invasive squamous cell carcinoma [10]. The prevalence of oncogenic subtypes of HPV (16/18) in oral cavity lesions is high in dysplastic lesions [11].

HPV and Squamous Cell Carcinomas of the Head and Neck

The relation between HPV and head and neck cancers was first described relatively recently by Syrjänen in 1983 [12-14]. This role of HPV in head and neck malignant tumors has demonstrated in the

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oral cavity, pharyngeal and laryngeal SCC. HPV is detected in 23% to 35% of all head and neck SCC, especially cancers that arising the oropharynx, in which HPV have been identified in 45% to 90% of all the cases [15-17]. The lingual and palatine tonsils are the most common sites where HPV was detected. With less frequency, HPV was identified in SCC of the oral cavity and the larynx. HPV 16 and, with less frequency, HPV 18, were identified in these carcinomas [18]. Similar to cervical cancer, HPV 16 is the most common type detected in 68% to 87% of all head and neck SCC [8,19].

Oral Squamous Cell Carcinomas and HPV Infection

The incidence of tonsillar and neoplasms of the base of the tongue is increasing in direct relation with HPV infection. Also, in these tumors, HPV 16 is the most frequent subtype identified (86% of cases) [20-22]. Increased number of oral sex partners have been associated with an increased risk of HPV infection; a similar situation occurs with vaginal or anal HPV-related lesions [23], and increases the risk of oropharyngeal SCC [24,25]. Additionally, HIV infection is an independent risk factor to a high prevalence of different grades of HPV lesions. Patients seropositive for HIV had a significantly high prevalence of oral HPV infection (25,3% vs 7,6%; p< 0,001) and oral high-risk of HPV serotypes (13,7% *vs* 4,5%; p 0,001) in comparison with HIV-negative individuals [26]. These findings suggest that immunodeficiency associated with HIV infection may increases the risk of oral HPV infection, and secondary, to oral SCC [27-29]. Clinically, HPV-associated oral SCC have different clinical and histopathological findings and an improve prognosis. These patients are typically younger, male, non-smokers and non-drinkers [30,31]. HPV-positive tumors are more frequently poorly differentiated and with a basaloid morphology in comparison with HPV-negative cancers [31,32]. Finally, patients with HPV oral SCC positive tumors generally presents with advanced disease and TNM stage [33,34]. Improved prognosis for HPV-positive patients with oral SCC presented with locally advanced disease could be achieved with a treatment based on chemotherapy and radiotherapy [35]. Also, a recent case report, described 2 patients with HPV-related anal SCC who subsequently developed oral SCC [36]. Generally, these secondary primary cancer occurs in patients with history of HPV related SCC, but originated in a different site of the first malignant lesion.

Also, Licitra et al [37] observed that HPV-positive patients with oral SCC treated primarily with surgical resection followed by adjuvant radiotherapy had a significantly improved 5-year overall survival rate (79% *vs* 46%; p= 0,00018). However, in a retrospective analysis at the Mayo Clinic, no significant survival difference was seen between HPV-positive and negative patients treated with surgery followed by radiotherapy [38]. Another retrospective studies, with transoral robotic surgery showed no differences in outcome according to HPV status [39,40].

HPV Infection and Esophageal Squamous Cell Carcinoma

The first reports that suggested a relationship between esophageal SCC and HPV-oncogenic subtypes infection date to 1982 [41]. Syrjänen was the first to suggest the association of HPV with both benign and malignant squamous cell lesions of the esophagus [42]. One of the most important characteristics of SCC of the esophagus is the wide variation in the incidence of the disease in different regions of the world [43].

Several risk factors have been described related with the development of esophageal SCC. Chemical or toxic substances, cigarette smoke, excessive alcohol intakes, and nutritional deficits of vitamins and other elements, have been linked to this malignancy [44,45]. More later, Syrjänen [42] suggested the possible role of HPV infection with the development of this neoplasm. Multiple studies detected HPV-DNA in esophageal carcinomas using different in situ hybridization (ISH) techniques and polymerase chain reaction (PCR). HPV detection rates ranged between 23% using ISH and 15% by PCR en esophageal cancers [42].

Similar to other SCC of the head and neck, oncogenic subtypes of HPV, especially 16, have a stronger relationship with the development of esophageal SCC. Additionally, the presence of serum antibodies against HPV-16 E7 oncoprotein should be a predictive factor of esophageal SCC [46]. Also similarity to other SCC of the head and neck, some data suggested that both E6 and E7 oncogenic proteins interfere with the cell cycle regulation and play an important role in the pathogenesis of esophageal SCC [42,46].

Conclusion

In conclusion, it is well demonstrated that HPV oncogenic subtypes are involvement in the pathogenesis of both, benign (papillomas or condylomas) and malignant (carcinomas) of the head and neck, including oral and esophageal lesions. HPV-DNA was detected by ISH and PCR in premalignant lesions and cancers in both, general and HIV infected patients. The experimental data suggest that similar pathogenic mechanisms to those occur in cervical and anal SCC is also implicated in head and neck HPV-associated SCC.

A higher suspicion is necessary to achieve an early diagnosis and to improve the survival of patients with head and neck carcinomas associated with HPV, especially in HIV-seropositive patients. A carefully evaluation of infiltrative or tumoral lesions of these anatomic region is necessary in this kind of patients. Finally, these patients show a lower risk of second primary cancers.

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