CASE REPORT

Malignant transformation of human papilloma viral lesion into squamous cell carcinoma of the tongue in the HIV population: Case reports and review of literature

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Summary Human papilloma virus (HPV) is the most common sexually transmitted viral disease responsible for mucosal warts and anogenital malignancies. HPV-associated oral lesions include condyloma, focal epithelial hyperplasia and some squamous cell carcinomas. Both oral and genital lesions caused by HPV are more commonly seen in those co-infected with HIV. While there is some degree of HPV genotypespecific clinical presentation, unusual manifestations of oral HPV disease in the HIV-positive patient frequently occur. Examinations of oral-wart biopsy specimens from HIV-positive individuals reveal a range of HPV genotypes, including cutaneous type 2; genital types 6, 11, 16 and 18; and oral type 13. However, the most common HPV genotypes identified in HIV-associated oral warts are oral specific HIV type 32 and the cutaneous HPV type 7. This paper presents two cases of HPV lesions associated with these types, which progressed into oral squamous cell carcinoma.

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Introduction

The human immunodeficiency virus (HIV) epidemic continues to grow at a significant rate worldwide with over 34 million people infected.¹ This disease leads to progressive immune suppression with selective depletion of CD4⁺ T lymphocytes. Numerous opportunistic infections occur secondary to this decrease in systemic immunity, particularly in the oral cavity with over 50% of HIV-infected individuals developing oral pathology.² One pathogen that is commonly found in both the oral and genital tracts of HIV-positive individuals is human papilloma virus (HPV).³ HPV is the most common sexually transmitted viral disease associated with mucosal warts and anogenital malignancies.⁴ HPV-associated oral lesions include condyloma, focal epithelial hyperplasia and some squamous cell carcinomas. Both oral and genital lesions caused by HPV are more commonly seen in those co-infected with HIV.⁵ While there is some degree of HPV genotypespecific clinical presentation, unusual manifestations of oral HPV disease in the HIV-positive patient frequently occur. Examinations of oral-wart biopsy specimens from HIV-positive individuals reveal a range of HPV genotypes, including cutaneous type 2; genital types 6, 11, 16 and 18; and oral type 13. However, the most common HPV genotypes identified in HIV-associated oral warts are oral specific HIV type 32 and the cutaneous HPV type 7. This paper presents two cases of HPV lesions associated with these types, which progressed into oral squamous cell carcinoma.

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patients is the mucosatropic human papillomavirus (HPV); however, HPV infection can occur with or without mucosal pathology.3,4 HPV-associated oral lesions include condyloma, focal epithelial and some squamous cell carcinomas.4,5 Both oral and genital lesions caused by HPV are more commonly seen in those co-infected with HIV.6–8 Systemic immune reconstitution for the HIV-positive patient has been accomplished with highly active anti-retroviral therapy (HAART), leading to decreases in systemic and oral infections, including regression in HPV-induced cervical lesions.9,10 Paradoxically, recent reports have noted increases in oral pathology consistent with HPV infection in the presence of HAART.11–13 Although the majority of the oral papillomas occur on the labial mucosa, they can also occur on the buccal mucosa, the tongue, the soft palate, and the gingiva. The histopathology of oral warts almost invariably demonstrates poorly differentiated, large, vacuolated koilocytic cells, but the gross appearance varies greatly.

A wide range of HPV genotypes in the HIV population has been identified and categorized by site of infection: cutaneous (2, 7), oral (13, 32) and anogenital (6/11, 16) genotypes.14 However, the most common HPV genotypes identified in HIV-associated oral warts are oral — specific HIV type 32 and the cutaneous HPV type 7. This paper presents two cases of HPV lesions associated with type 32, which progressed to squamous cell carcinoma.

HPV DNA detection process

DNA extraction was performed using a multiplex PCR reaction containing HPV L1-consensus primers (PGMY09/11) and β-globin primers (GH20/PC04) (supplied by: Roche Molecular Systems) to test for sample adequacy (Fig. 1). Quality assurance and contamination avoidance was performed by using separate areas for DNA extraction, PCR set-up and gel electrophoresis. For each PCR run, a master PCR mix was prepared, and water blanks were inserted after every fourth sample. After amplification, products were analyzed by electrophoresis, and the size of the band obtained was compared with the molecular weight standard. DNA extracted from cultured SiHa cells was used as a HPV+ positive control. PCR products after 40 amplifications were considered positive for HPV, if the products demonstrated the 254 base-pair β-globin band and the ~450 base-pair HPV band.

Case #1

A 43-years old Caucasian male presented to the dental clinic at the Medical Center of New Orleans, Louisiana, with an indurated mass on the tongue. The mass slowly increased in size over a 5-month period in the left anterior region of the tongue. The patient’s medical history was significant for HIV, manic depression, cholecystectomy, and neurosyphilis. The CD4 count was 120 and the viral load was 28 000. The patient was presently on a regimen of Highly active Antiretroviral therapy: nevirapine (Viramune; Boehringer Ingelheim Corporation, Connecticut, USA), ritonavir (Kaletra; Abbott Laboratories, Illinois, USA) and abacavir (Ziagen; Glaxosmithkline, Munich, Germany). There was no history of smoking, drug abuse or family history of cancer.

Review of systems was unremarkable with no otalgia, dysphagia, odynophagia, hoarseness, or coughing. His physical examination was unremarkable except for a 2 × 3 cm ulcerative, indurated, mass in the left anterior tongue (Fig. 2). Cranial nerves II–XII were intact with no paresthesia. There was no fixation of tongue, lymphadenopathy or uvula deviation. The parotid and submandibular ducts were all patent. The CT scan of the face, neck, and chest showed the mass on the tongue with no lymph node involvement or other masses present. The TNM staging system identified the tumor as T2N0M0. Blood electrolytes and CBC were all within normal limits. There was no evidence of any opportunistic active infections. There were no other lesions noted in the oral cavity at the time of biopsy.

The patient underwent an incisional biopsy of the mass in the left anterior tongue. The diagnosis of the incisional biopsy was well-differentiated, invasive, keratinizing squamous cell carcinoma (Figs. 3 and 4). DNA extraction using the polymerase chain reaction (PCR) showed only HPV type 32 to be present (Fig. 1).

Case #2

A 33-years old African–American male presented to the Oral Surgery clinic at the Medical Center complaining of pain while chewing due to a mass on the tongue, which progressively increased in size over a 7-months period (Fig. 5). The medical history was significant for HIV and Hypertension. The patient had a CD4 count of 246 and an undetectable viral load. The patient was presently on ritonavir (Kaletra; Abbott Laboratories, IL, USA), abacavir (Ziagen; Glaxosmithkline, Munich, Germany) and efavirenz (Sustiva; Bristol Myers
Squibb, Chicago, USA). There was no history of tobacco or illicit drug use or any family history of cancer. Review of systems was unremarkable with no otalgia, dysphagia, odynophagia, hoarseness, or coughing. His physical examination was unremarkable except for a 3·4 cm ulcerative, indurated, and mass in the left ventral–lateral region of the tongue (Fig. 5). Cranial nerves II–XII were grossly intact, but the left side of the tongue was mildly paresthetic. The tongue was adequately fixed to the floor of the mouth with no abnormal function. The parotid and submandibular ducts were all patent with normal salivary flow. The CT scan of the face, neck and chest showed the mass on the tongue with no lymph node involvement or other masses present. The stage of the tumor was classified as T2N0M0. No abnormality was detected in the blood electrolytes. The patient also did not exhibit any underlying opportunistic infections or any active infections.

The patient underwent an incisional biopsy under local anesthesia and the diagnosis was consistent well-differentiated, invasive, keratinizing squamous cell carcinoma (Figs. 6 and 7) DNA extraction using the polymerase chain reaction (PCR) showed only HPV type 32 to be present (Fig. 1).
Discussion

Oral squamous cell carcinoma (OSCC) is the most common cancer of the oral cavity. Although use of alcohol and tobacco are two known risk factors, some evidence indicates that other factors, such as infection with certain HPV subtypes and genetic susceptibility, could also be involved in the carcinogenic process. HPV types 16 and 18 were declared as human carcinogens by the International Agency for Research on Cancer. They are the most important single etiological agents of cervical squamous cell carcinomas. However, their relationship to OSCC is not well-defined. The high prevalence of human papillomavirus (HPV) infections and associated morbidity among persons infected with human immunodeficiency virus (HIV) have only recently been recognized.

This increase in the occurrence of oral warts may be significant because of the greater numbers of HIV-positive individuals surviving longer due to successful HAART therapy. Malignant transformation of cervical lesions or anal condylomas in HIV-positive individuals could have significance for the development of HPV-related oral cancers. Development of HPV-associated malignancies occurs over significant periods of time, and prior to the introduction of HAART, many HIV-positive individuals died of AIDS-related illnesses, but due to HAART and the subsequent increased longevity of this population we may see an increase in HPV-related pathology. Condylomas of the anus are commonly considered as benign lesions, but oncogenic types of HPV have been detected within anal carcinoma cells, which raises the issue of the role that these viruses may play in the progression of condyloma to invasive carcinoma. HIV infection is thought

Figure 4  Higher power view of the same lesion seen in Fig. 3 showing malignant cells easily recognizable as being of squamous cell carcinoma.

Figure 5  3 × 4 cm indurated mass on the left ventrolateral surface of the tongue extending to the floor of the mouth.

Figure 6  Low power photomicrograph showing hyperparakeratotic surface and cords of poorly differentiated epithelial cells streaming downward from the surface epithelium.

Figure 7  High-power view of the same lesion seen in Fig. 6 showing invading islands of malignant cells with focal keratin formation recognizable as being squamous cell carcinoma.
to increase the risk of anal carcinoma by 30 times. In several studies, tonsillar and oropharyngeal carcinomas contained HPV DNA more commonly than cancers at other head and neck sites.21,22

Preliminary analysis has identified HPV-32 as the predominant genotype found in oral warts in the New Orleans HIV+ cohort.23 Investigators think that asymptomatic oral HPV infection occurs frequently but that oral warts occur infrequently, presumably due to immunological control of the virus. The critical aspects of the immune response that prevent the progression from asymptomatic HPV infection to HPV disease are unknown, but previous studies have focused on HPV genotype-specific response against the major capsid protein, L1. The increased rate of HPV-related oral pathology seen in HIV-positive patients highlights the need for a more thorough understanding of the immune response to oral HPV infections. This paper presents two cases of HPV lesions associated with type 32, which progressed to squamous sell carcinoma.

References