Prevalence and risk factors for oral human papillomavirus infection in Mexican HIV-infected men

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Abstract

Objective. To determine the prevalence and risk factors for oral high-risk human papillomavirus (HR-HPV) infection in *human immunodeficiency virus (HIV)-infected* men. **Materials and methods.** Consecutive male outpatients with HIV-infection were enrolled. Demographic and behavioral risk data were obtained. Anal swabs and oral rinses were tested for HR-HPV DNA. Oral, pharyngeal and video laryngoscopy examinations were performed for detection of lesions. **Results.** The prevalence of HR-HPV oral infection was 9.3% (subtypes other than HR HPV 16/18 predominated). The prevalence of anal HR-HPV infection was 75.7%. The risk factors for oral infection with HR-HPV were tonsillectomy (OR=13.12) and years from HIV diagnosis (OR=1.17). **Conclusions.** Tonsillectomy and years from HIV diagnosis were associated with oral HPV infection. No association was found between oral and anal HR-HPV infections. This is the first study reporting the prevalence and risk factors for oral HR-HPV infection in Mexican HIV-infected population.

Keywords: human papillomavirus; head and neck cancer; human immunodeficiency virus

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Resumen

Objetivo. Determinar la prevalencia y los factores de riesgo para infección oral por virus de papiloma humano de alto riesgo (VPH-AR) en individuos con VIH. **Material y métodos.** Se incluyeron pacientes ambulatorios consecutivos con VIH. Se recabó información demográfica y sobre factores de riesgo conductuales. Se detectó DNA de VPH-AR en hisopado rectal y enjuague bucal. Se efectuó exploración de boca, faringe y videolaringoscopía para detectar lesiones. **Resultados.** La prevalencia de VPH-AR oral fue 9.3% (predominaron subtipos diferentes de VPH-AR 16/18). La prevalencia de VPH-AR anal fue 75.7%. Los factores de riesgo para VPH-AR oral fueron la tonsilectomía (OR=13.12) y los años de diagnóstico del VIH (OR=1.17). **Conclusiones.** La tonsilectomía y los años de diagnóstico del VIH se asociaron con VPH-AR oral. No hubo asociación entre VPH-AR oral y anal. Este es el primer reporte sobre prevalencia y factores de riesgo para VPH-AR oral en población mexicana con VIH.

Palabras clave: virus de papiloma humano; cáncer de cabeza y cuello; virus de inmunodeficiencia humana

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The oropharyngeal squamous cell carcinoma (OPSCC) is usually observed in older adults and is associated with tobacco and alcohol consumption.[1] With a different clinical and epidemiological profile, the human papillomavirus (HPV)-related cancer is a particular form of OPSCC, with risk factors related to sexual behavior.[2,3]

Over the last 40 years, an increasing incidence of HPV-related cancers in adults under 60 years of age has been observed.[4] In fact, the rise in HPV-related OPSCC has reached epidemic proportions.[5] HPV-related cancer is caused by high-risk subtypes (HR-HPV), namely 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 58;[6] while benign HPV subtypes, most commonly 6 and 11, are responsible for condyloma acuminata and respiratory papillomatosis.[7]

Previous studies have shown an increased prevalence of HR-HPV in HIV-infected population (13.7%), compared to non-HIV-infected adults (4.5%).[8] Indeed, the incidence of HPV-associated cancers in HIV infected individuals is also higher,[9] and the risk of oropharyngeal cancer is 2 to 6-fold greater than in the general population.[10] Although the aforementioned increased rates are poorly understood, risk factors for HPV-associated cancers include HIV-associated immune deficiency and higher incidence and persistence of HPV infections.[9]

While increases in HPV-unrelated OPSCC might be related to improvements in life expectancy for HIV-infected population, the natural history, the prevalence and risk factors of oral HPV infection and HPV-related OPSCC are largely unexplored. Therefore, the aim of our study was to determine the prevalence and risk factors for HR-HPV oral infection in Mexican HIV-infected individuals without oral cancer.

Materials and methods

Study population

This prospective, cross-sectional study was conducted at the *Centro de Investigación en Enfermedades Infecciosas, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas* (INER), a national referral center in Mexico City for HIV-infected patients. The study was conducted during the period between January 2014 to January 2016, and followed the principles of the Declaration of Helsinki. The protocol was approved by the Research and Ethics Committee of the INER (Approval No. C46-12). Written informed consent for patient information and images to be published was provided by the patients. Consecutive male outpatients with HIV infection aged 18 years and older were included. Demographic and behavioral risk factors were assessed by using a questionnaire. Collected data included age, sexual behavior, tobacco and alcohol use, and HIV-related history. In order to detect lesions in the upper airway, oral and pharyngeal visual examinations were performed, as well as a video laryngoscopy (Storz 90° rigid endoscope). All patients underwent a neck examination through palpation for detection of palpable cervical lymph nodes.

Sample collection

Samples for HPV testing from the oral mucosa were obtained by swishing 10 mL of sterile saline solution for 10 seconds and gargling for five seconds. Samples were stored at -80°C within 15 minutes of collection. HPV testing was performed with the Abbot Real Time High Risk HPV (Abott Molecular Inc., Illinois, USA), a clinically validated test that allows genotyping of HPV 16, HPV 18 and pooled detection of twelve HR- HPV genotypes: HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.

Blood samples were collected by antecubital vein puncture under fasting conditions. Vacutainer EDTA 4 ml blood collection tubes were used for measurement of CD4 T cell counts by flow cytometry, with the TruCount CD4+ assay (Becton- Dickinson, Franklin Lakes, New Jersey, USA). Vacutainer EDTA 6 ml blood collection tubes were used for determination of plasma HIV RNA loads, with the Abott Real Time HIV-1 assay (Abott Molecular Inc, Illinois, USA).

Histopathologic examination of biopsies

Histopathologic examination was performed using standard procedures. Samples were fixed in phosphate-buffered formaldehyde for six hours, and dehydration was done with a gradual series of ethyl alcohol and finally with xylol. Microtome-cut sections of paraffin-embedded samples were stained with hematoxylin-eosin for microscopic examination.

Statistical analysis

Demographic categorical data were compared by using Fisher's exact test. Wilcoxon rank-sum test was used to compare continuous variables. All statistical analyses were performed using SPSS version 20 (SPSS Inc, Chicago, Illinois, USA). A 2-sided p value <0.05 was considered to be significant. Only variables with a p value ≤ 0.05 in the univariable analysis were included in multivariable analyses.

Results

Demographic and clinical characteristics

One hundred and seven HIV-infected outpatients underwent oral HR-HPV testing. The median age was 36 years (interquartile range [IQR], 30–44). The median nadir CD4 T cell count was 54 CD4 T cells/mm^3, and the median CD4 T cell count on HR-HPV testing was 402 CD4 T cells/mm^3 (IQR 263–552). One hundred and one individuals (94.4%) were receiving antiretroviral therapy at study enrollment. Clinical characteristics are shown in table I. None of the patients had received the HPV vaccine. Ten individuals (9.3%) had HR-HPV oral infection (95%CI, 3.85-15.38%). Of those, 7 (6.7%) had subtypes other than HR HPV 16/18 infection (subtypes 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68); 2 had HPV 16 infection (1.9%); and one individual had HPV 16 and a subtype other than HR HPV 16/18 co-infection (1%). None of the patients had HPV 18 oral infection. Eighty-one patients (75.7%) had HR-HPV anal infection (95%CI, 67.44-83.96%). Eight individuals had both anal and oral HR-HPV infections. Of those, six had the same HR-HPV subtype in anus and oral cavity. No association was found between oral and anal HR-HPV infections (Fisher's exact test, p=0.48). Two individuals (1.9%) had papillomas in the oral cavity, probably caused by the low-risk HPV subtypes 6 or 11 (figure 1), and none of them had concomitant HR-HPV oral infection. Five individuals had palpable cervical lymph nodes. Histopathologic examination of biopsies revealed HIV-associated lymphadenopathy in all cases. Seven individuals had other oral, pharyngeal or laryngeal lesions not related to HPV in the physical examination: two had Kaposi's sarcoma (one in the hard palate and the other in the larynx); one had laryngeal nodules, one presented villous leukoplakia; one had aphtous stomatitis; one had vocal cord paresis, and one had post-intubation laryngeal stenosis.

Risk factors

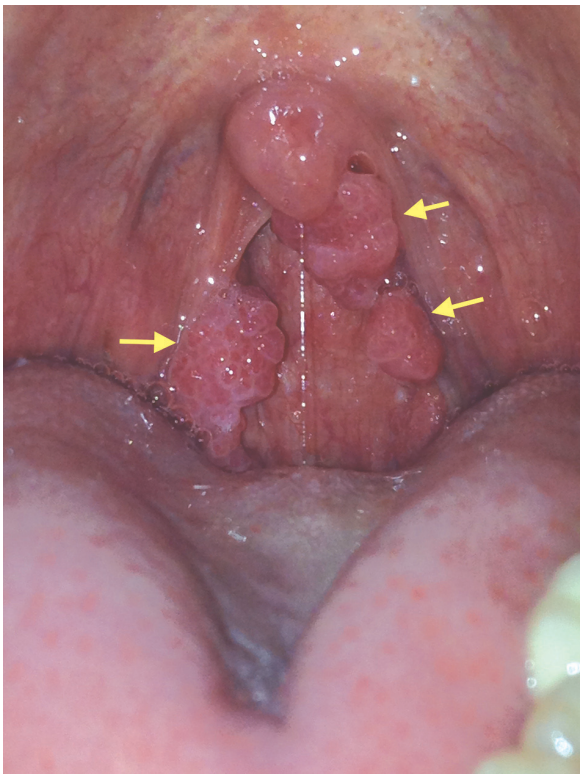
Univariate analysis indicated that oral HR-HPV infection was associated with low nadir CD4 T cell counts (p=0.050), years from HIV diagnosis (p=0.001) and tonsillectomy (p=0.015) (table I). However, in the multivariate analysis only years from HIV diagnosis (OR = 1.17, 95%CI = 1.04–1.31) and tonsillectomy (OR = 13.12; 95%CI = 1.56–109.97) remained significant. No association was found between oral HR-HPV and former or current smoking, alcohol abuse, age of first intercourse, number of sexual partners in lifetime or in the last year, being a man who has sex with men, or oral sex.

Table I
CHARACTERISTICS OF HIV-INFECTED INDIVIDUALS INCLUDED IN THE STUDY

Characteristic	*Oral HR-HPV Positive (n=10)*	*Oral HR-HPV Negative (n= 97)*	*p value*
Age (median, years, IQR)	42.5 (35–47.25)	35.5 (29.75–44)	0.164
CD4 T cell count (median, IQR)	319.5 (254–552.25)	403 (263–567)	0.533
CD4 T cell count nadir (median, IQR)	42.5 (12.25–52.5)	60 (27.25–242)	0.050
Time since HIV diagnosis (median, years)	4	3	0.001
ART (%)	100%	94.7%	1.000
Undetectable HIV RNA load	77.8%	76.1%	1.000
Former or current smoking	63.8%	90%	0.274
Alcohol abuse	20%	19.4%	0.961
Age of first intercourse (median, IQR)	16 (13.75–18.5)	16 (13–18)	0.813
Sexual partners (median, IQR)	30 (4.75–70)	15 (7–50)	0.937
Sexual partners in the last year (median, IQR)	1 (1–3)	1 (1–2)	0.767
MSM	80%	88%	0.471
Oral sex*	100%	84.7%	0.210
Tonsillectomy	30%	3.6%	0.015

* No subject reported consistent condom use

HR-HPV: High-risk Human papillomavirus; MSM: Men who have sex with men; ART: Antiretroviral therapy; IQR: Interquartile range
Procedures were performed during the period between January 2014 to January 2016, at the *Centro de Investigación en Enfermedades Infecciosas, Instituto Nacional de Enfermedades Respiratorias*



Procedures were performed during the period between January 2014 to January 2016, at the *Centro de Investigación en Enfermedades Infecciosas, Instituto Nacional de Enfermedades Respiratorias*

Figure 1. Squamous papillomas (arrows) in the right posterior tonsillar pillar and the posterior pharyngeal wall

Discussion

Anal HR-HPV infection has been extensively studied in Mexican population, but to our knowledge, this is the first study reporting the prevalence and risk factors for oral HR-HPV infection in Mexican HIV-infected men. We found a lower prevalence of HR-HPV oral infection in HIV-infected individuals than previous reports.[8,11,12] This discrepancy could be attributed to the different distribution of HPV subtypes across geographic regions.

In contrast to earlier findings, current or former smoking was not a risk factor for oral HR-HPV infection in our study. Our results are consistent with those describing an association of tonsillectomy with persistent HPV oral infection.[13] This could be explained by the fact that tonsillar tissue is an important site of immune induction and surveillance in the upper aerodigestive tract.[14] It was reported that tonsillectomy leads to decreased incidence of tonsillar squamous cell carcinoma (SCC),[15] but arguments against prophylactic tonsillectomy include the fact that patients would still have a risk of cancer in the base of the tongue; the constant contact to the same sexual partner may result in reinfection; the clinical implications of remote tonsillectomy are still unknown; the risk of clonal expansion and migration of HPV-infected cells to other sites, and recent data that implicate tonsillectomy as the cause of increased risk of cancer in other organs.[16]

Our results corroborate the association between oral HR-HPV infection with low CD4 T cell counts in HIV-infected population described in previous studies.[17,18] Years from HIV diagnosis would aggravate the immunocompromised status derived from HIV-infection, contributing to the persistence of HPV infection. However, the mechanism by which immunosuppression contributes to oral HPV infection is not well understood.

The lack of association between oral and anal HR-HPV infections may have a multifactorial origin. It is well known that HPV subtypes have specific affinities for different tissues. Also, sexual practices are diverse, so oral-anal or only anal intercourse may occur. The number of sexual partners may also be variable. Thus, the lack of correlation between oral and anal HR-HPV infections may indicate different routes and moments of transmission.

A limitation of this study is that it has a cross-sectional design, and not all variables associated with oral HPV were addressed, and not all confounders were controlled. Moreover, by measuring oral HPV infection at only one time-point, transient acquired infection cannot be distinguished from persistent or latent infections. A second limitation was that we did not control for teeth brushing, and recent tooth brushing increases HPV detection in oral rinses.[19] An additional limitation was that despite oral rinse sampling is a highly sensitive method, it is not suitable for distinguishing between oral cavity infection and oropharynx infection.

It is well known that HPV has a relevant role in head and neck SCC (HNSCC), as it is responsible for up to 45 to 90% oropharyngeal cancers.[20] HPV 16 in particular, is the causative agent for 25% of HNSCC.[21] However, unlike cervical cancer screening, for which CDC recommends immediate colposcopy if HPV 16/18 test is positive,[22] there are no guidelines for oral HR-HPV detection, especially in high-risk population such as HIV-infected individuals.

Conclusions

We found a prevalence of oral HR-HPV infection of 9.3% in Mexican HIV-infected men. Years from HIV diagnosis and tonsillectomy were strongly associated with HR

HPV oral infection. Further work is required to define the clearance rate, the natural history of oral HR-HPV, the incidence of HNSCC and the role of tonsillectomy in HIV-infected population.

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Supporting information

Research data. A file with the minimal anonymized data set necessary to replicate our study findings is available upon request to the authors.

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

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