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Chapter

Correlation and Diagnosis of Human Papilloma Virus (HPV) Manifestations in Male or Female Genitalia and Oral Cavity

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Abstract

The prevalence of the human papilloma virus (HPV) in the oral cavity and oropharynx has not been well elucidated yet. The aim of this study was to correlate the concomitance of prevalence of HPV in genitalia of men and women with or without HIV/Aids, having manifestations in the oral cavity. Dentist's (DS) attention is justified by the increase in *Condylomata acuminatum* in the oral cavity and the possible correlation of manifestations in patients' genitalia. When associated with seropositivity for HIV/Aids, it becomes an important cofactor increasing the possibility of manifestations of the disease in view of the diminished immunity of these patients. The prevalence and concomitance of the percentage of *C. acuminatum* lesions in genitalia were correlated with those in the oral cavity by using the following variables: gender, age, skin color, category of exposure, habits, general and oral diseases, presence or absence of xerostomia, T-CD4 lymphocytes, and viral load. The results showed the prevalence of 7 (17.95%) for those who presented concomitant genital/oral lesions. Both the experience and results must become public, aiming to disseminate knowledge about the degree of complexity of the epidemic and need for preventive measures to ameliorate propagation of the disease in the population.

Keywords: human papilloma virus, oral and genital manifestations, sexually transmitted disease, oral medicine, oral diagnosis

1. Introduction

The human papilloma virus (HPV) is the cause of *Condylomata acuminatum* lesions (derived from the Greek word Kondilus = round tumor, and Latin word acuminare = to become pointed), also called genital or common warts. This is a

non-cultivable DNA virus, belonging to the Papovaviridae family. It is a small virus, 55 nm in diameter, without an envelope, with 72 capsomers in a capsid with icosahedral symmetry, formed of non-enveloped, double-stranded circular DNA made up of approximately 7200 to 8000 base pairs. HPV presents a high degree of tropism for epithelial and mucosal tissue, seeing the viruses are found in lesions of the oral and nasal cavity, connective tissue, paranasal sinuses, larynx, tracheobronchial mucosa, esophagus, ureter, anogenital tract, and skin [1–5].

At present, genital infection by HPV is the most frequent sexually transmitted viral disease (STD) in the sexually active population throughout the world, and it is transmitted by direct contact from person to person, with periods of incubation from 50 to 150 days. Progression from the incubation stage to active expression depends on cellular permissiveness, type of virus, and immunological status of the host, remembering that immunosuppressive agents such as cancers, HIV/Aids and others favor contagion and development of the disease. The capacity for contagion persists for several years and fewer than 10% of individuals present subclinical infections. Transmission of HPV to the oral mucosa occurs by self-inoculation though the practice of oral sex, multiplicity of partners, promiscuity, lack of hygiene and harmful habits, such as smoking and consuming alcoholic beverages, play a role in the modifying and facilitating factors in transmission of the disease, interfering negatively in the response to recommended treatments [6–11].

The clinical manifestations of human papilloma virus (HPV) in the oral cavity have hardly been investigated by dental surgeons, and many authors consider the oral cavity an important reservoir and source of infection of this virus. Infections caused by HPV are generally of the exophytic growth type and proliferate in papillary projections. They may be pediculated or sessile, presenting as multiple, small, reddened, pinky or whitened nodules that increase over the course of time, and are frequently confluent, normally shown by their “cauliflower” aspect [1, 9, 12–17].

In the oral cavity, HPV is responsible for four types of diseases, squamous papilloma, vulgar wart, *C. acuminatum* and focal epithelial hyperplasia. Tongue is the most frequent site of lesions due to HPV, followed by palate, oral mucosa, gingiva, lips, tonsils, uvula, and mouth floor. Of the over 200 subtypes of HPV identified, 24 have been associated with oral lesions (HPV-1, 2, 3, 4, 6, 7, 10, 11, 13, 16, 18, 30, 31, 32, 33, 35, 45, 52, 55, 57, 59, 69, 72, 73), 16 with HPV and 17 being the most prevalent in both oral and genital lesions meaning that it might be related to oro-genital transmission. Pairs 6 and 11 are also those that are most found, affecting keratinized or non-keratinized areas, also remembering that HPV 16 and 18 are the most oncogenic, and have been proven to be responsible for neck cancer, uterus and carcinomas in the oral cavity. In the oral mucosa, the prevalence of HPV and its role in the pathogenesis of dysplasias and cancer have been elucidated, suggesting the oral cavity to be a reservoir of this virus and infection in combination with other factors such as cigarettes and alcohol favor the later development of neoplasia [2, 4, 5, 8, 10, 13, 15, 16, 18–21].

Human papilloma virus in the oral mucosa has been diagnosed by clinical exam, cytology, biopsy, immunohistochemistry, DNA hybridization, hybrid capture and PCR (polymerase chain reaction). The cytological aspect of HPV infection is characterized by two criteria, with the larger being shown by Koilocytes with perinuclear haloes (cytoplasmic vacuolation) and nuclear dysplasias; and the smaller type by dyskeratocytes, metaplasia, macrocytes, and binucleation. Biopsy allows for histopathological study of a sample representative of the lesion, to confirm and grade the lesion, but does not identify the type of HPV, which is obtained only by means of molecular biology techniques (*in situ* hybridization, hybrid capture and PCR

(polymerase chain reaction). PCR consists of a technique that has revolutionized virology, due to its extremely high sensitivity, capable of detecting up to one viral genome in 100,000 cells, and is the most sensitive method of detection. Another two widely used methods that have equivalent sensitivity are hybrid capture and PCR with general primers. This type of PCR is potentially capable of detecting all the mucosal HPVs [9, 12, 18, 20–26].

The acquired immunodeficiency syndrome (Aids) is the manifestation of infection by the human immunodeficiency virus (HIV)—manifestations of both general and laboratory signs, symptoms and results that indicate immunological deficiency or failure. Aids led to the union among researchers in all areas of health to seek greater knowledge but have not yet convinced dental surgeons of the vital importance of measures for infection control. During infection by HIV, the immunodeficiency resulting from chronic infection of T-CD4 cells by the virus culminates in the appearance of opportunist infections and some neoplasia [4, 11, 14, 16, 17, 19, 22–24, 27–29].

As there are few studies in patients with diagnosis of orogenital and oral cavity manifestations, which consider factors such as immunosuppression and highly active antiretroviral therapy (HAART), the aim of this study was to correlate the concomitance of the prevalence of HPV in the genitalia of men and women with or without HIV/Aids, diagnosed in the public health care services for patients with STD/Aids, in São Paulo, with clinically and laboratory confirmed manifestations in the oral cavity at the Study and Care Center for Special patients of the University Paulista – São Paulo, making public the experience and results, with a view to disseminating knowledge with regard to the degree of complexity of the epidemic and need for preventive measures to ameliorate the propagation of the disease in the population.

2. Methods

Patients with a diagnosis of *C. acuminatum* lesions in genitalia, and those referred to the Specialized Care Services of STD/Aids, to Dental Care Services of CEAPE UNIP – (Study and Care Center for Special patients of the University Paulista – São Paulo), were evaluated in a quantitative approach, by means of epidemiological, clinical, documentary, and cross-sectional research. The prevalence and concomitance of the percentage of *C. acuminatum* lesions in genitalia were analyzed and correlated with those in the oral cavity by using the following variables: gender, age, skin color, category of exposure, habits, general and oral diseases, presence, or absence of xerostomia, T-CD4 lymphocytes, and viral load.

The research project, including informed consent document, was approved by the Ethics Committee on Research in Human Beings, protocol CEP 642/09 - UNIP – SP.

- Inclusion criteria:
 - Presence of one or more *C. acuminatum* lesions in the anogenital region - body or Glans penis, scrotum, inguinal, intraurethral or perianal/anal, vaginal regions - clinical or subclinical.
 - Patients with clinical and histological exams of *C. acuminatum* in genitalia.
 - Male and female sex

- Age between 18 and 60 years.
- HIV/AIDS patient.
- Exclusion criteria:
 - Patients with fasting glycemia higher than or equal to 126 mg/dL;
 - Patients with diagnosis of lymphoproliferative system disease, such as leukemia and lymphoma, identified by means of a Physician's report.
 - Patients with immunosuppressive drug therapies such as corticoids, cyclosporin, azathioprine, and tacrolimus, among others.

To enable the work to be done, each patient was previously verbally informed about the clinical and laboratory exams to be performed, the term of free and informed consent was then delivered to the patients and signed by them if the patients agreed to do so.

The oral cavity was examined by naked eye, with the help of artificial light provided by the dental reflector. Once an oral lesion was identified, excisional biopsy of the lesion was performed under local anesthesia with 2% Lidocaine. The material was placed in a tube containing 10% formol and sent to the Oral Pathology Department of UNIP, SP, for histological study. The material was processed by embedment in paraffin and submitted to sectioning in a rotary microtome, thus obtaining 4 μm -thick cuts. Histological cuts stained with hematoxylin and eosin were performed and submitted to histological exam.

2.1 Saliva collection

Saliva was collected with the volunteers fasting for a minimum period of 2 hours, at the recommended time of 14:00 hours. The individuals had to be positioned in a seated and relaxed manner.

The whole saliva of individuals was collected by mechanical stimulation, by masticating 1 piece of paraffin (10 × 10 cm, weighing approximately 1.4 grams, available in the Dentobuff® kit). All saliva produced in the first 30 seconds was discarded (swallowed or expelled), and the sample saliva was collected for exactly 5 minutes. Throughout the time of the procedure, the individual continued chewing and expelling saliva into a graded glass beaker (Dentobuff® Kit Dentobuff®).

2.2 Salivary flow/secretion speed

Salivary flow was determined by means of the ratio between the volume collected to the time of 5 minutes. The salivary secretion speed was demonstrated in milliliters per minute. (mL/min). When the flow speed was high, the time of 5 minutes was reduced, and when it was low, the time was increased (in general, the individual chewed gum for at least 2 minutes, or then 2 ml of saliva was collected). The salivary volume was divided by the collection time and compared with a flow evaluation table. Example: 5 ml collected in 5 minutes—1 ml/min.

According to the Dentobuff® kit manufacturer, normal salivary flow ranges between 1.6 and 2.3 ml/min. Intermediate salivary flow (moderate), between 1.0 and 1.5 ml/min. and low salivary flow (severe)—less than 1.0 ml/min.

All the patients were offered a questionnaire that was applied when they consented and were predisposed to respond, which evaluated: sexual practices (oral and anal); number of present and previous sexual partners in the last year; frequency of sexual activity; presence of absence of previous HPV and other sexually transmitted diseases; safe sex or not (use of condoms); personal history of genital lesions due to HPV; harmful habits (drugs, smoking, consumption of alcoholic beverages).

As treatment option, patients with a single (isolated) or up to two lesions were submitted to complete surgical excision of the lesion(s), proceeding with asepsis of the field, local anesthesia with 2% lidocaine, removal by means of scalpel, and/or use of TCA—90% Trichloroacetic acid (TCA) for multiple lesions, applied with a cotton bud imbibed in removing the excess, and deposited with great care and light touches on the lesions, observing the change in color as they became whitened in a tenuous manner on the area contemplated, facilitating visualization and confirming the recommended treatment.

3. Results

All the patients presented genital warts, proved clinically and by histological study of the anogenital samples, which showed findings suggestive of *C. acuminatum*.

Of the 24 patients examined by the Dental Surgeon, 5 (20.83) presented concomitant genital/oral lesions (please see **Table 1**).

18 (75%) of the men, of whom 11 (61.11%) were homosexual; 7 (63.64%) smokers and 3 (27.27%) alcohol consumers) and 7 (38.89%) heterosexual (2 (28.57%) smokers) and 6 (25.00%) women, of whom 4 (100%) heterosexual (2 (33.33%) smokers). (please see **Table 2**).

Of the 24 patients, 14 (58.33%) were undergoing HAART administration. Of these 14 patients, 3 (21.43%) presented T-CD4 cells <200 cell/mm³ of blood, 2 (14.29%), of 201 to 499 cell/mm³ of blood and 9 (64.29%), above 500 cell/mm³. Furthermore, among the 24 HIV/Aids patients, 10 (41.67%) presented an undetectable viral load, 11 (45.83%) up to 20 thousand copies, and 3 (12.50%), over 20 thousand copies.

As regards general diseases, 3 (12.50%) patients presented with diabetes mellitus, 2 (8.33%) tuberculosis, 2 (8.33%) hepatitis B and C, 2 (8.33%) syphilis, 2 (8.33%) psychiatric disorders 1 (4.17%) neurotoxoplasmosis.

Presence of Concomitant Lesions			
Group	No	Yes	Total
HIV-	13 (86.67)	2 (13.33)	15 (100.00)
HIV+	19 (79.17)	5 (20.83)	24 (100.00)
Total	32 (82.05)	7 (17.95)	39 (100.00)

p = 0.686

Table 1.

At level of significance of 5% shows the distribution of frequencies of the variable presence of concomitant lesions is the same in the two groups (P-value >5%).

Group	Gender	Hetero	Homo	Total
HIV-	Female	4 (100.00)	0 (0.00)	4 (100.00)
	Male	7 (63.64)	4 (36.36)	11 (100.00)
HIV-	Female	6 (100.00)	0 (0.00)	6 (100.00)
	Male	7 (38.89)	11 (61.11)	18 (100.00)
Total		24 (61.54)	15 (38.46)	39 (100.00)

Table 2. Distribution of frequencies of variable sexual behavior by group and gender (the percentages obtained per line are shown in parentheses).

With regard to oral diseases, 6 (25%) presented candidiasis in its various forms (pseudomembranous, erythematous, and angular cheilitis), 5 (20.83%) periodontal diseases (gingivitis, periodontitis, necrotizing ulcerative periodontitis and linear gingival erythema), 2 (8.33%) herpes simplex, 2 (8.33%) aphthoid ulcers (minor and major) and 1 (4.17%) hairy leukoplakia. As regards age, 7 (29.17%) patients were in the 2nd decade of life, 13 (54.17%) in the 3rd, and 4 (16.67%) in the 4th decade of life. There was the presence of xerostomia in a severe and moderate grade in 5 (20,83%), light grade, and normal in 19 (79.17%) patients.

In response to the questionnaire, the following were evaluated:

- Sexual practices (oral and anal): 25 (64.10%) patients reported practice of oral sex, and of these, 22 (88%) reported anal sex.
- Numbers of present and previous sexual partners, in the last year: 11 (28.21%) responded interaction with the same partner (only), 18 (46.15%) with up to 5 different partners, and 9 (23.08%) more than 6 partners per year.
- Frequency of sexual activity, 14 (35.90%) practiced 1 (once) a week, 15 (38.46%) 2 or 3 times and 10 (25.64%) over 4 times a week.
- Presence or absence of HPV and other previous sexually transmitted diseases: 7 (17.95%) previously had some STD.
- Safe sex or not (use of condoms): 24 (61.54%) used them regularly, 8 (20.51%) sometimes, and 7 (17.95%) never.
- Personal history of genital lesions due to HPV: 4 (10.26%) had lesions at some time.
- Harmful habits (drugs, smoking, alcohol): 17 (43.59%) smokers, 5 (12.82%) alcohol consumers and 3 (7,69%) other illegal drugs.

All patients with oral manifestations (**Figures 1–3**) were included in the surgical treatment protocol or topical application of 90% TCA, and of these patients, 1 (2.56%) were submitted to surgical removal of the lesion, and 6 (15.38%) were



Figure 1.
Clinical exophytic HPV lesion in interdental papilla in the space of missing element 22.



Figure 2.
Clinical exophytic/pedicated HPV lesion on the right side of the mandible.

treated with 90% TCA. Of the patients treated with TCA, the mean number of applications of the medication was in three session (every 7 days), but in three smoker patients, the mean number of applications was 5 times. In the patient who underwent surgical removal of the lesion there was recurrence, and in the six patients with multiple manifestations, in 3 (50%) of them other episodes of recurrence occurred. In five (12.82%) homosexual patients with a CD4 level below 200 to 500 cells/mm³ of blood, more exuberant recurrences of lesions were observed, and greater difficulty in obtaining effective responses to topical treatment with 90% TCA. These patients were followed-up during the period of 1 year.



Figure 3.
Multiple HPV flat lesions on the upper lip.

4. Discussion

The human papilloma virus (HPV) are viruses capable of producing skin and mucosal lesions, and the main means of contagion continues to be the sexual pathway. It is also possible to become infected through blood, the vaginal opening, kissing, objects of personal use, or any other infected objects [1–5].

Diagnosis of HPV in the oral mucosa may be suspected by clinical exam of the lesion, cytology, and biopsy, however, the molecular biology exams are those capable of detecting the DNA of HPV in the cell, with polymerase chain reaction (PCR) being outstanding as the most sensitive technique for researching HPV. Establishing the etiological role of HPV in oral lesions and evaluation of different techniques for HPV detection are of fundamental importance.

There are controversies about the prevalence of HPV in the oral mucosa because various research have pointed out a wide variety of results, pointing out discrepant variations in the HPV rates detected, perhaps due to the number of samples of patients researched, which vary greatly, or even as a result of the techniques used for diagnosis. Various other factors contribute to increasing the prevalence of human papilloma virus in the oral cavity, with the drop in the patient's immunological defense against the virus, or even in HIV/Aids patients, in addition to the number of partners, practice of oral sex and failure to use condoms confirmed in our research, being important facilitating and modifying factors for the increase in chances of contamination and infection by HPV, its dissemination and recurrence. [9, 12, 18, 20–26].

Self-inoculation may be a means of HPV transmission; that is, from infections in the skin and anogenital region, infection may occur in the oral cavity, however, there are discussions and questions with respect to the importance of these modes of propagation of infection by HPV to the oral cavity. Over the last few years, great interest has been aroused in the international scientific community about attention to tracking infection by HPV in other anatomic sites, in parallel to anogenital infection, to elucidate whether genital infection by this virus may be a predisposing factor

for infection of other sites, such as the oral cavity. Therefore, it is believed that the existence of anogenital infection by HPV appears to be a predisposing factor for oral infection by HPV, which is in agreement with this research, in which there was proof by both clinical means and histological study of the anogenital samples that showed evidence of finding suggestive of *C. acuminatum*. Of the 39 patients examined by the Dental Surgeon, 7 (17,95%) presented concomitant genital/oral lesions. It is of fundamental importance that patients with genital HPV must be extremely concerned about transmitting the virus to their partner(s) and to other sites in their body. [2, 6–11, 25].

Greater clinical and scientific basis is necessary to establish the relationship between genital and oral HPV and their implications in the daily clinical activities of the dental surgeon. The oral cavity plays a role as important in sexual relations as in genital relations, and it is important to know the tie between the presence of virus in these sites, to make early diagnosis, and prevent greater complications, particularly the development of carcinomas in the oral cavity, a possibility that has been scientifically proved.

Previous infection by HIV seen in the progression of infection by the virus, and representing advanced clinical characteristics of Aids, or even at the beginning or on conclusion of HAART, has been shown to be a modifying or determinant factor regarding opportunist infections. These factors act as markers of the states of immunodeficiency, leading the patient to seeking treatment, normally because of the discomfort, esthetics, and visible severity of immunosuppression, measured by the TCD-4 lymphocyte levels that act as a determinant factor in the progression of HIV. [4, 11, 14, 16, 17, 19, 22–24, 27–29].

5. Conclusion

Supported by the data obtained in this research, which correlated the concomitance of HPV prevalence in genitalia with manifestations in the oral cavity, and the wish to make public the experience and results, with a view to disseminating knowledge with regard to the degree of complexity of the epidemic, and the need for preventive measures, in order to ameliorate the propagation of the disease in the population, allowed us to draw the following conclusions:

- The frequency of the appearance of oral HPV concomitant with genital manifestations was 17.95%.
- Further explanations and dissemination of information about prevention and early detection of both oral and genital HPV to the population are necessary, and with special emphasis on young adolescents, in an endeavor to diminish the incidence of contamination, eradication, and propagation of the disease.
- Between partners relevant warnings must be given about implementing preventive behaviors, seeking early diagnosis and or treatment recommended for each case.
- HIV is an important modifying and facilitating risk factor for infections and the development of lesions in the oral cavity due to HPV, showing evidence of more exuberant lesions with greater difficulty in responding to treatments.

- The habit of smoking inhibits and makes clinical regression of lesions difficult in response to the recommended treatment.
- Therefore, further studies are necessary, increasing the number of patients researched, to confirm the results obtained in this study, to obtain less interference in the results, and greater elucidations about infection by HPV and its prevalence in the oral cavity.

Conflict of interest

The authors declare that they have no conflicts of interest.

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