

Local control of human papillomavirus infection after anal condylomata acuminata eradication

Controle local da infecção perianal pelo papilomavirus humano após a erradicação dos condilomas acuminados

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A B S T R A C T

Objective: To verify whether the eradication of anal condylomata acuminata was effective for local control of HPV infection using anal colposcopy and anal brush cytology. **Methods:** We evaluated 147 patients treated for anal margin and/or anal canal condyloma, with 108 HIV-positive and 39 HIV-negative individuals. The average age for males was 40 years for HIV-positive and 27.5 for HIV-negative. In females, the mean age was 37.5 years for HIV-positive and 31.5 for HIV-negative. **Results:** Twenty-four patients (16.3%) had normal cytology and anal colposcopy, 16 (10.9%) normal cytology and altered anal colposcopy, 52 (35.4%) normal anal colposcopy and altered cytology, and 55 (37.4%) had altered cytology and anal colposcopy. **Conclusion:** the eradication of clinical lesions failed to locally control HPV infection.

Key words: Mass screening. Papillomavirus infections. Neoplasms. Anal canal. Cell biology.

INTRODUCTION

The human papillomavirus (HPV) is the most common among the various sexually transmitted etiological agents that cause disease in the anogenital region¹. For Brazil, the World Health Organization (WHO) estimates the appearance of 684,400 new cases annually². Its incidence has been increasing in recent years, associated with acquired immunodeficiency syndrome (AIDS)³, being / diagnosed between 15.7% and 62% of patients in different series¹. It mainly affects men who have sex with men (MSM)^{1,3}.

To date, more than 200 HPV types have been identified; 45 of them infect the anogenital region⁴. Oncogenic types are strongly related to the etiology of tumors of the anogenital tract and its precursor lesions⁵ and can be isolated in approximately 80-93% of anal carcinomas, the type 16 being the most frequent^{6,7}.

Most HPV infections have no clinical consequence. However, 10% of patients will develop warts, papillomas or dysplasias⁸. It is believed that this fact depends on the level of individual virus resistance, systemic immunity and local factors, including local immunity⁸. The condition is not unique to immunocompromised individuals, but is most common when the serum T CD4 + lymphocyte count is below 500/ μ L⁹. The exclusively anal location is typical of

MSM due to the use of the anorectal segment to provide erotic pleasure¹⁰.

The difficulty of treatment, the high incidence of recurrence and the possibility of carcinomatous transformation, especially among the immunocompromised, are features of HPV. By reviewing the literature, we found recurrence rates between 10 and 88%, depending on treatment^{10,11}. It is difficult to differentiate cases of reinfection, though. There are those who associated relapses to the presence of latent infection in apparently normal epithelium¹². Hence the importance of long-term follow-up and implementation of protocols to control the disease.

The possibility of detection of remaining or recurrent lesions, as well as the precursors of anal carcinoma, suggests that there should be instituted standardized screening and follow-up programs to prevent infection and decrease recurrence by HPV in patients at risk.

The cytology of the anal canal with brush has been performed¹³⁻¹⁶ with similar efficacy to the cervix collection¹⁷, and has a sensitivity ranging between 42 and 98% and specificity ranging from 38 to 96%, when results were compared with histology^{13,17,18}. Many authors recommend it as a method for screening populations at high risk for anal carcinoma¹⁹⁻²¹.

The anal colposcopy, having been recently introduced in the diagnostic arsenal for the specialty, is yet

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to have its indications well defined. Most Physicians carry it out as a screening method to identify the most appropriate sites for biopsy when after altered cytology. It has also been suggested for screening of precancerous lesions due to cost-effectiveness in risk groups, amongst those the immunosuppressed^{20,21}.

To date, the literature has not provided enough evidence for anal colposcopy and anal brush cytology to be used as forms of follow-up of treated patients to detect subclinical remaining lesions. Moreover, one cannot assess whether the treatment of condylomata acuminata was enough to eradicate HPV infection, preventing relapses and progression to carcinoma. Thus, we decided to check whether the eradication of anal condylomata acuminata is effective in local control of HPV infection using anal colposcopy and anal canal brush.

METHODS

We retrospectively analyzed data from patients seronegative and seropositive for HIV attended in the outpatient clinics after eradication of anal lesions caused by HPV. The visits occurred between March 2009 and October 2011 at the clinic of Proctology of the Emilio Ribas Institute of Infectious Diseases.

This study was approved by the Ethics in Research Committee of the Emilio Ribas Institute of Infectious Diseases under number 428/2009.

The sample consisted of 147 patients treated for condylomata acuminata of the anal margin and/or the anal canal. A hundred and eight were HIV seropositive, with 101 men and seven women, and 39 seronegative, 19 men and 20 women. The mean ages were 40 years for HIV-positive men and 27.5 years for HIV-negative. Among women, 37.5 years for HIV-positive and 31.5 years for HIV-negative.

We chose to include patients over 18 years, who had no clinical lesions caused by HPV 30 days after its eradication, obtained with clinical treatment associated or not with surgery, and pathological diagnosis confirming the anal HPV infection. We excluded patients who had the material of anal canal brush cytology from the two samples classified as inadequate or insufficient by the pathologist, and those with clinical recurrent or persistent lesions of the anal margin or anal canal.

Warts were diagnosed clinically with proctologic exam, which consisted of static and dynamic inspection, perianal palpation, rectal examination and anal colposcopy. Digital rectal examination and anal colposcopy were not performed when the disease covered the anal margin, which could cause pain and bleeding. Tissue samples were collected and subjected to histological examination to confirm clinical diagnosis.

The clinical treatment consisted of weekly applications of an ointment of 25% podophyllin in

petrolatum on lesions of the anal margin and 90% trichloroacetic acid on lesions above the dentate line. Patients were evaluated after four applications and those with lingering injuries were referred to operative treatment. The verrucous lesions were sectioned with scissors, close to the skin, and hemostasis of bleeding points was made by electrocoagulation. Very small lesions were treated by electrofulguration. Warts' specimens were then sent to pathological examination.

Patients who showed no signs of disease 30 days after the eradication of anal warts were selected for follow-up, which consisted of two samples of anal cytology with brush and anal colposcopy with 3% acetic acid.

The findings of cytology were distributed in unsatisfactory or satisfactory and in this case, according to cellularity, following the classification of Bethesda^{22,23}. We considered the result with the highest degree of dysplasia for definitive diagnosis, regardless of it being observed in the first or second sample.

The findings of the anal colposcopy were divided into negative, when there were no changes, and positive when there were white lesions in the anal margin and/or anal canal.

We submitted the results to statistical analysis with the non-parametric Mann-Whitney test and the parametric Student's t and chi square tests. We considered the tolerance < 5% for all statistical tests.

RESULTS

Statistical analysis using the chi-square test revealed more men in the HIV seropositive population and equal incidence of genders in the group of seronegative ($p < 0.0001$).

Statistical analysis using the Student t test showed that HIV-positive men were more advanced in age than HIV-negative ones ($p = 0.037$). There was no significant age difference between the seropositive and seronegative women ($p = 0.282$), nor between seropositive ($p = 0.559$) and seronegative ($p = 0.295$) men and women.

The findings of the cytology of the anal canal are shown in table 1.

The findings of the anal colposcopy are shown in table 2.

Patients evaluated were divided into four groups according to the findings of anal cytology and colposcopy (Table 3).

The group with unchanged anal colposcopy and normal cytology consisted of 24 patients, five women and 19 men, aged 19 to 54 years, with mean 36.7. They were 11 seronegatives and 13 seropositives, with CD4 counts ranging from 204 to 780/mL.

The group with altered anal colposcopy and normal cytology consisted of 16 patients, three women and

13 men, aged from 20 to 55 years, mean 35.6. Five were seronegative and 11 seropositive, with CD4 counts ranging between 300 and 938/mL.

The group with normal anal cytology and altered colposcopy consisted of 52 patients, 12 women and 40 men, aged between 16 and 64 years, mean 38.7. Sixteen were seronegative and 36 seropositive, with CD4 counts ranging from 88 to 1463/mL.

The group with abnormal anal cytology and colposcopy was comprised of 55 patients, seven women and 48 men, aged between 18 and 60 years, mean 37.1. There were seven seronegatives and 48 seropositives, with CD4 counts ranging from 200 to 1058/mL.

Comparison of mean serum counts of CD4 T lymphocytes of HIV-positive patients with and without subclinical lesions showed no statistical difference (Mann-Whitney test – $p = 0.704$). The presence of subclinical lesions was not associated with scores above and below 500/mL in HIV-positive patients ($p = 0.771$).

Table 1 - Findings of the anal canal brush cytology during follow-up.

Cytological findings	n°	%
Negative	40	27,2
LSIL	65	44,2
HSIL	41	27,9
ASCUS	01	0,7
Total	147	100

LSIL – low grade squamous intraepithelial lesions

HSIL – high-grade squamous intraepithelial lesions of

ASCUS – atypical squamous cells of undetermined significance

Table 2 - Anal colposcopy findings during follow-up.

Anal Colposcopy findings	n°	%
Negative	76	51,7
Injury in AC	30	20,4
Injury in AM	22	15
Injury in AC and AM	19	12,9
Total	147	100

AC- anal canal

AM- anal margin

Table 3 - Distribution of the results of anal colposcopy and of the anal canal brush cytology during follow-up.

	Normal colposcopy	Altered colposcopy
Normal cytology	24 (16,3%)	16 (10,9%)
Altered cytology	52 (35,4%)	55 (37,4%)

DISCUSSION

Our study evaluated more HIV-positive men than women, and similar numbers regarding gender among seronegatives. These data were expected because the number of men with HIV is four times higher than women in our country².

Regarding age, we observed that the group of seronegative men was the youngest. As we know that infection among men tends to maintain over time, and that it is more present in women up to 30 years of age²⁴, we expected that the group of seronegative women to be the youngest. We suspect that the small number of women in the sample is responsible for this observation. On the other hand, among seropositive individuals the average age of men and women was similar, probably because the immunosuppression caused by HIV contributed to perpetuate HPV infection.

Although many authors recommend anal colposcopy and cytology as screening methods^{13-19,25}, we have used the association of both methods to follow-up after treatment of anal HPV-induced lesions²⁶. There is no universally accepted protocol that defines the period to perform anal colposcopy and cytology of the anal canal after eradication of warts. We indicated the exams 30 days after the end of treatment, when we observed no visible disease, a time sufficient to healing of wounds, preventing them from being confused with those of viral origin²⁶. We also wanted to reduce discomfort during the exam, associated to the fact that during this period the patient would unlikely be reinfected, since he/she would be in convalescence. If the examination is normal, we recommend semiannual reassessments until three of them are normal. Some authors cite intervals of three²⁷ and six months²⁸ in the first year for follow-up and even annual screening tests²⁹.

The present series allowed to define the period of one month as sufficient for the detection of subclinical lesions after eradication of warts. However, we believe that the expansion of the series will give strength to the evidence of current results.

In a previous study, when comparing the results of the cytology of the anal canal with one and two samples, we noted that the sensitivity with two samples was higher than the single collection and the specificity was similar²⁶. For this reason, we adopted the two collections as a routine.

In our study, anal colposcopy showed HPV-induced lesions in the anal canal and anal margin in 48.3% of patients examined. In other 35.4%, the colposcope examination was normal, although cytology was altered. These facts showed that HPV infection was not completely controlled in 83.7% of patients. We found no published work with which we can compare these results. We also seek to assess whether HIV infection determines more relapse or more remaining lesions. But the small number of HIV-negative patients in the sample prevented this analysis.

When the condition is detected, treatment is initiated for controlling clinical relapses and preventing progression to malignancy. However, when the disease is evidenced only by cytology, it becomes impossible to define a therapy, because we do not know where the injuries are and we do not consider correct the application of topical agents on, or surgical resection of, random areas. Additionally, there may be false-positive results, as proven by an earlier study³⁰. Anyway, we understand that the anal canal can be a reservoir of infection, and that at an appropriate time, usually when immunity falls, the diseases caused by this virus may reappear. Moreover, the colposcope is unable to visualize the interior of the crypts. If there is remaining infection in this location, it will not be detected by this method. However, cells with pattern of squamous intraepithelial lesions (SIL) that have been detached can be

captured by the brush, altering the result of cytology. For these reasons, we chose the combination of cytology and colposcopy examination with acetic acid and suggest that these methods should not be used alone in follow-up.

Recurrences are more frequent among those with lower CD4 + T lymphocytes²⁹. In the present study, the seropositive patients had more subclinical lesions at follow-up. However, the comparison of mean serum counts of CD4 +²⁹ T lymphocytes in HIV-positive patients with and without subclinical lesions showed no difference, and the presence of subclinical lesions was not associated with scores above and below 500/mL, showing that immunity did not influence this effect.

We intend to continue this study by assessing whether the presence of oncogenic HPV types would increase the rate of recurrent or remaining subclinical lesions in the treated patients. We are also concerned about the outcome of patients with normal anal colposcopy and abnormal anal brush cytology, for whom we are developing further study.

The results obtained in the present study, in which we perform anal brush cytology and anal colposcopy for follow-up of patients treated for anal condylomata acuminata, showed that eradication of clinical lesions did not locally control the infection with human papillomavirus and that periodic control should be instituted.

R E S U M O

Objetivo: verificar se a erradicação dos condilomas acuminados perianais foi efetiva no controle local da infecção pelo HPV, utilizando a colposcopia anal e a citologia anal com escova. **Métodos:** avaliamos 147 pacientes tratados de condiloma da margem e/ou canal anal, sendo 108 HIV-positivos e 39 HIV-negativos. A média etária no sexo masculino foi 40 anos para os HIV-positivos e 27,5 anos para os HIV-negativos. No sexo feminino, a média etária foi 37,5 anos para os HIV positivos e 31,5 anos HIV-negativos. **Resultados:** vinte e quatro pacientes (16,3%) apresentavam citologia e colposcopia normais, 16 (10,9%) citologia normal e colposcopia alterada, 52 (35,4%) citologia alterada e colposcopia normal e 55 (37,4%) citologia e colposcopia alteradas. **Conclusão:** a erradicação das lesões clínicas não controlou localmente a infecção pelo HPV.

Descritores: Programas de rastreamento. Infecções por papillomavirus. Neoplasias. Canal anal. Biologia celular.

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