

Diagnostic Methods for Prevention of Anal Cancer and Characteristics of Anal Lesions Caused by HPV in Men with HIV/AIDS

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Abnormalities found with anoscopy under colposcopic vision, anal cytology and anal biopsy were evaluated in 21 men with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) at the Federal University of Pernambuco Hospital in Brazil. Mean age was 38.4 ± 6.0 years, and mean time of HIV infection was 8.3 ± 5.1 years; 95.2% of the patients had been on highly active antiretroviral therapy (HAART) for an average of 6.6 ± 4.5 years. Mean CD4+ cell count was 482.2 ± 173.75 cells/mm³, and 80.9% presented a HIV viral load of $< 5,000$ copies/mL. Reported sexual preference was 52.4% homosexuals, 28.6% bisexuals, and 19.0% heterosexuals; 81% reported having had receptive anal intercourse and 61.9% reported more than 10 sexual partners of the same sex. Results of anoscopy under colposcopic vision revealed 17 (81.0%) low-grade lesions and/or condylomata or micropapillae and four (19.0%) high-grade lesions with or without condylomata. Among the 21 anal cytology examinations, seven (33.3%) revealed low-grade squamous intraepithelial lesions (LSIL); three (14.3%) presented atypical squamous cells of undetermined significance (ASCUS) and 11 (52.4%) were normal. Seventeen patients were submitted to anal biopsy with the following findings: three patients (17.6%) with normal epithelium, one (5.9%) with infection by HPV, three (17.6%) with condylomatas, two (11.8%) with AIN 1, four (23.6%) with AIN 2, three (17.6%) with AIN 3, and one (5.9%) with AIN 2. Anoscopy under colposcopic vision was found to be useful for detecting anal lesions and for guiding anal biopsies. Anal cytology was less useful, as it underestimated the frequency of lesions.

Key-Words: HIV/AIDS, HPV, anoscopy, anal cytology, anal biopsy.

Individuals infected by the human immunodeficiency virus (HIV) have a high risk of infection by human papillomavirus (HPV), as well as a high incidence of anal intraepithelial neoplasia (AIN) and anal cancer caused by HPV [1]. The potentialization of the effects of HIV by HPV is not fully understood [2]. These changes may be due to a deficient response of the immune system due to HIV or direct interaction between HIV and HPV [2-4].

In recent years, strong evidence for the participation of HPV in the pathogenesis of anogenital cancer has been found. High-risk HPVs are found in more than 99.7% of cervical squamous cell carcinomas. In anal cancer patients, the frequency of detection of high-risk HPVs ranges from 70 to 100%, depending on origin, location, sexual orientation and HIV status [5].

Anal cancer has similar biological properties to cervical cancer. Like the cervix, the anal canal has a transformation zone in which the columnar epithelium of the rectum joins the squamous epithelium of the anus. As in the cervical transformation zone, the anorectal junction is a common site of anal HPV infection and development of AIN, a potential precursor of anal cancer. Anal intraepithelial and cervical neoplasias present the same histological patterns, are associated with the same types of HPV, and have a similar natural history [6,7].

Transmission and acquisition of HPV infection occurs through the mucocutaneous epithelial tissue, as a result of lesions that occasionally are provoked by the sexual act, or through the thin epithelial layers, such as the transition zone of the cervix and the anus. The virus becomes stable in the undifferentiated basal layer of the epithelium, a region that HPV requires to begin infection. The life cycle of HPV depends on continuous replication of the host cell; the virus uses the machinery of the infected cell for replication of its genetic material and expression of oncoproteins [5].

In view of the biological and epidemiological similarities between cervical and anal squamous carcinomas mediated by HPV and the significant reduction in the incidence of cervical cancer after the implementation of oncotic cytology in recent decades [1,8], anal examination of high-risk groups, such as HIV-positive patients has been recommended [1,8-11]. Oncotic cytology and anoscopy under colposcopic vision are the main techniques recommended for the detection of anal cancer.

The technique of anoscopy under colposcopic vision is similar to that of cervical colposcopy [12]. Suspicious areas become acetowhite with the application of acetic acid, and vascular alterations manifest as punctations and mosaics. Abnormal epithelium does not stain dark brown with lugol (iodine solution) staining, as observed in normal squamous epithelium [1]. Anoscopy under colposcopic vision is extremely valuable for determining the extent and characteristics of anal and perianal intraepithelial lesions [13].

We compared various methods to detect anal lesions mediated by HPV (anoscopy under colposcopic vision, anal cytology and anal biopsy) and examined the characteristics of these lesions in a group of men with HIV/AIDS.

Received on 6 April 2008; revised 20 July 2008.

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Material and Methods

We made a case series study in the Infectious and Parasitic Diseases Outpatient Clinic and in the Colposcopy and Lower Genital Tract Department (CIGTD) of the University Hospital of the Federal University of Pernambuco (HC-UFPE) from July to November 2006. The study population consisted of 21 male patients with HIV/AIDS who presented anal lesions detected by anoscopy under colposcopic vision, with or without abnormalities based on anal cytology and biopsy. These patients were part of a group of 60 individuals with HIV/AIDS enrolled in a prevalence study of anal lesions caused by HPV. Patients received information about their examination, and those who agreed to take part in the study signed an informed consent document.

After the questionnaire had been filled out, the patients' clinical records were consulted to record their latest T CD4+ lymphocyte counts and viral load data. T CD4+ lymphocyte counts were measured by the flow cytometry method. The viral load, based on HIV (RNA-HIV) ribonucleic acid particles, was quantified by the nucleic acid sequence-based amplification (NASBA) method.

Anal cytology was performed with a cytological brush, moistened with a saline solution, introduced into the anal canal to a depth of between 3 and 5 cm, rotated 360° and removed in a spiral movement. The material adhering to the brush was rolled onto a dry transparent glass slide and conditioned in a cylindrical recipient containing 95° ethyl alcohol as a fixing solution. The slides were stained by the Papanicolaou pap-smear method (with hematoxylin-eosin dye) and examined under light microscopy by a single cytopathologist. The cytological findings were classified in accordance with the Bethesda system (2001) for the classification of preinvasive cervical and anal lesions [14]. The intraepithelial anal lesions were classified as low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL) or atypical squamous cells of undetermined significance (ASCUS).

After the cytology collection, anoscopy was performed with a colposcope; the patient was maintained in the right lateral decubitus position, with knees bent over the thighs. The anoscope was lubricated with aqueous gel and inserted; after removal of the embolus, 3% acetic acid was applied and the area was magnified and visualized with the colposcope. This procedure allowed identification of changes in the epithelium, characterized as a flat or dense acetowhite epithelium, associated or not with fine or thick punctuation/mosaicism. Next, Schiller's test was performed (application of a lugol solution). The anoscopic features were assessed using Barcelona Colposcopic Terminology [15].

Anoscopic findings suggestive of an anal lesion were biopsied. The biopsy procedure was guided by the colposcope with the aid of a Gaylor-Medina clamp, under local anesthesia using 2% lidocaine gel, without a vasoconstrictor. Whenever

an extensive macroscopically-visible lesion was found on the anal margin, a biopsy was conducted in the operating room under rachidian anesthesia. The histological evaluation was always made carried by the same pathologist and classified as one of the following: normal, atypical related to infection by HPV, condyloma acuminatum or intraepithelial anal neoplasia grade I, II or III [16].

The Bethesda System terminology (2001) is also applied to histological nomenclature; it classifies condylomata/HPV and AIN 1 as a low-grade squamous intraepithelial lesion and AIN 2 and 3 as a high-grade squamous intraepithelial lesion [13]. When we found lesions of different grades in the same patient, the highest grade lesion was considered. The anal biopsy was used to grade the anal and perianal lesions.

This study was approved by the Ethics in Research Committee of the Federal University of Pernambuco's Center of Health Sciences, protocol number 109/2006 – CEP/CCS.

Results

Age, clinical status of HIV infection and sexual preference of the patients are shown in Table 1. The mean age was 38.4 ± 6.0 years, the mean time since HIV infection diagnosis was 8.3 ± 5.1 years and HAART use was reported by 95.2%, with a mean duration of 6.6 ± 4.5 years. The mean T CD4+ lymphocyte count was 482.2 ± 173.75 cells/mm³; 80.9% had a viral load below 5,000 copies/mL. Sexual behavior was distributed as follows: 11 (52.4%) were homosexuals, six (28.6%) were bisexuals and four (19.0%) were heterosexuals. Eighty-one percent reported having had receptive anal intercourse and 61.9% reported having had more than 10 sexual partners of the same sex during their lifetime.

Results of Anoscopy Under Colposcopic Vision

Among the 21 patients with abnormal anoscopy, 10 (47.6%) presented low-grade anal lesions, demonstrated by flat acetowhite epithelium, negative iodine or with partial capitation of iodine at the anal squamous-columnar junction, associated or not with a fine mosaic, fine punctuation, micropapillae and concurrent endoanal and perianal condyloma acuminatum. Only one patient (4.8%) presented micropapillae at the anal squamous-columnar junction without acetowhite epithelium. Six patients (28.6%) presented only condylomatous lesions (Figure 1); one of them had a giant condyloma (Figure 2, Table 2).

Four (19.0%) patients presented high-grade anal lesions, three of whom presented an area of dense acetowhite epithelium associated with a thick mosaic. One patient presented concomitant high-grade anal lesions and endo and perianal condylomata (Table 2).

Anal Oncotic Cytology

Among the 21 patients with abnormal anoscopic findings, 11 (52.4%) presented normal cytological results, seven (33.3%) presented LSIL and three (14.3%) presented ASCUS (Figures 3 and 4, Table 3).

Table 1. Distribution of the 21 patients according to age, clinical state of HIV infection and sexual behavior.

Characteristics	N	%	Mean	SD
Age (years)				
28–40	12	57.1	38.4	±6.0
41–51	9	42.9		
Time of HIV diagnosis (years)				
0–5	6	28.6	8.3	±5.1
6–10	9	42.8		
11–18	6	28.6		
Antiretroviral use				
Yes	20	95.2		
No	1	4.8		
Time of use of antiretroviral (years)				
1–5	6	30.0	6.6	±4.5
6–9	10	50.0		
≥10	4	20.0		
CD4+ (cells/mm ³)				
<200	1	4.8	482.2	±173.75
200–500	8	39.1		
>500	12	57.1		
Viral load (copies of RNA/mL)				
<5,000	17	80.9		
5,000–30,000	3	14.3		
>30,000	1	4.8		
Sexual preference				
Homosexual	11	52.4		
Bisexual	6	28.6		
Heterosexual	4	19.0		
Receptive anal intercourse				
Yes	17	81.0		
No	4	19.0		
Numbers of partners of same sex (during life)				
None	4	19.0		
1–5	3	14.3		
6–10	1	4.8		
More than 10	13	61.9		

SD=standard deviation.

Anal Biopsy

Among the 21 patients indicated for biopsy due to abnormal anoscopic findings, four refused to undergo the procedure. Among the 17 on whom the biopsies were performed, three (14.3%) proved normal, six (28.6%) presented low-grade anal lesions caused by HPV-infection, condylomata (Figure 5A and B) and AIN 1, and eight (38.1%) presented high-grade anal lesions, represented by AIN 2, AIN 3 and PAIN 2 (Figure 6, Table 3).

Correspondence Between the Colposcopic Anuscopy Exams, anal Cytology and Biopsy

A comparison of the results of anuscopy under colposcopic vision, anal cytology and anal biopsy is shown in Table 3. Among the 10 (47.6%) patients with anoscopic findings of a low-grade anal lesion, only four (19.0%) presented a cytological

diagnosis of LSIL. Nine of these patients were submitted to biopsy, of which two (9.5%) had low-grade anal lesions and four (19.0%) had high-grade anal lesions.

Among the six (28.6%) patients with isolated condylomata, the cytology proved to be abnormal in two (9.5%) cases. The histological findings were low-grade anal lesions in three (14.3%) and high-grade anal lesions in one (4.8%). In one patient with micropapillae at the anal squamous-columnar junction seen in anuscopy, the cytology was normal and the biopsy showed an atypical pattern due to infection by HPV.

Four (19.0%) patients presented anoscopic findings suggestive of high-grade anal lesions. Anal cytology identified two (9.5%) diagnoses of LSIL and two (9.5%) of ASCUS. Three (14.3%) of these patients were submitted to biopsy and all three presented high-grade anal lesions. The four individuals who refused the biopsy had a normal cytological result and ASCUS.

Figure 1. Endoanal condylomata.

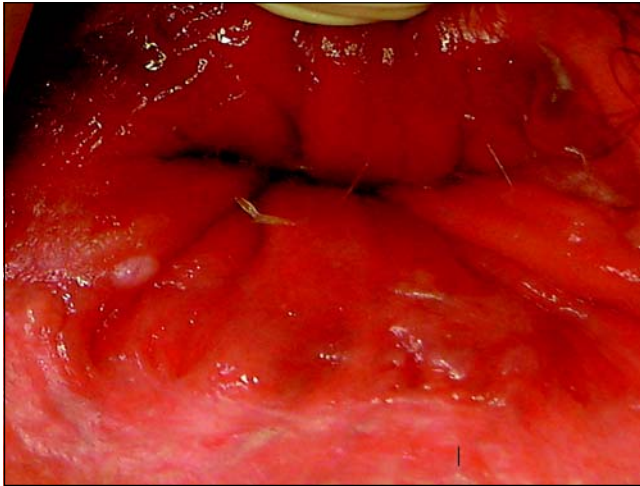


Figure 2. Gigant perianal condylomata.



Figure 3. Anal cytology of atypical squamous cells of undetermined significance – ASCUS.

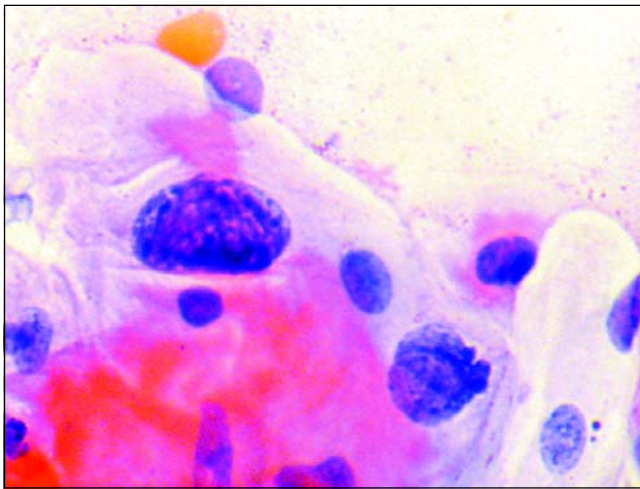


Figure 4. Anal cytology of low-grade squamous intraepithelial lesions – LSIL.

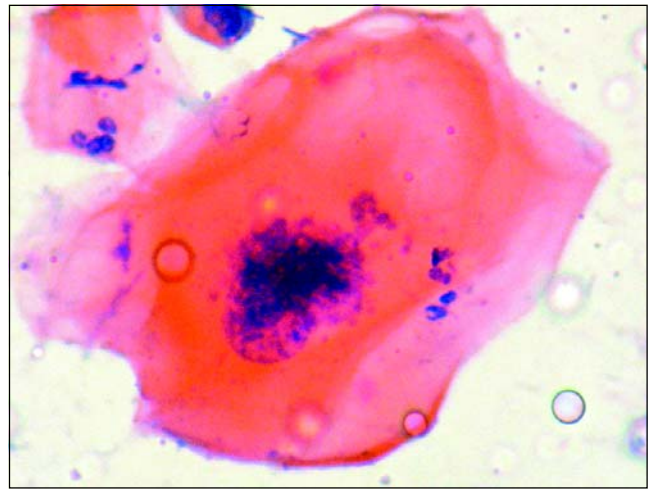


Figure 5. A: Transformation zone with papillomatose lesion rich in coilocytos (HE, 100x). B: Squamous epithelium hiperplasic.

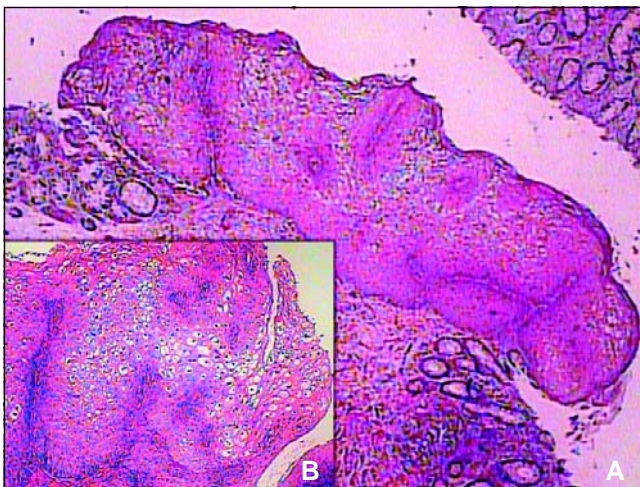


Figure 6. Neoplasm atipia in all malpighiano epithelium (AIN 3) (HE, 400x).

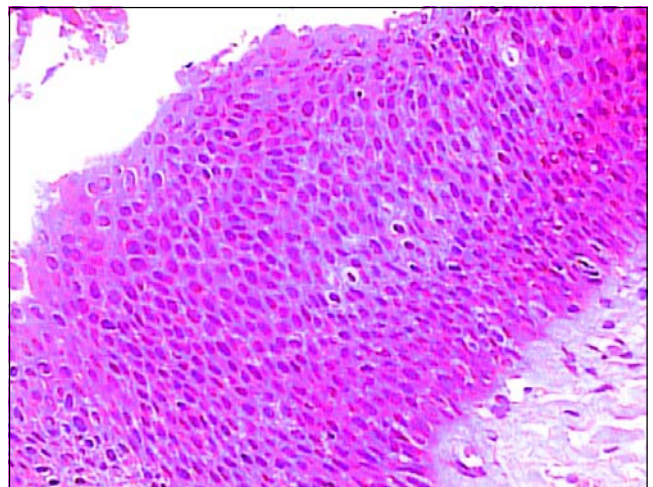


Table 2. Results of anoscopy under colposcopic vision

Results	N	%
Findings suggestive of low-grade lesion	10	47.6
Flat acetowhite epithelium	2	
Flat acetowhite epithelium with fine mosaic	2	
Flat acetowhite epithelium with micropapillae	1	
Flat acetowhite epithelium + endoanal condylomata	2	
Flat acetowhite epithelium + endo and perianal condylomata	1	
Flat acetowhite epithelium with fine punctuation + endo and perianal cond.	1	
Flat acetowhite epithelium with fine punctuation + endoanal cond.	1	
Finding suggestive of high-grade lesion	4	19.0
Dense acetowhite epithelium with thick mosaic	3	
Dense acetowhite epithelium with thick mosaic + endo and perianal cond.	1	
Condylomata acuminatum	6	28.6
Endoanal	2	
Perianal	1	
Endo and perianal	3	
Micropapillae	1	4.8
Total	21	100.0

Discussion

We conclude that anal examination of patients with HIV/AIDS is important for the detection of premalignant lesions and that anoscopy under colposcopic vision and histology is better than anal cytology for the diagnosis of these lesions. Although there is no consensus on the best way to screen for anal cancer [17], we suggest anal cytology, followed by biopsy, guided by anoscopy under colposcopic vision, for the prevention and diagnosis of anal lesions mediated by HPV in high-risk groups, such as men with HIV/AIDS [18,19].

The patients enrolled in our study were young, with a mean age of 38.4 years, a finding similar to those of Varnai et al. and Wilkin et al., who observed that anal lesions mediated by HPV occurred mainly in young individuals, with a mean age of 42.2 years for men with a histological diagnosis of anal lesion [20] and 40 years or less as a risk factor for abnormal anal cytology and biopsy [21].

When we examined the clinical status of HIV disease, our patients generally had a good immunological status. This favorable immunological profile was a result of their treatment, which not only decreased mortality, but also increased incidence of anal cancer and other HPV-associated diseases due to their longer survival, a finding already described by other authors [11,19,21,22]. The use of HAART does not seem to modify the natural history of HIV-HPV co-infection [4,19,23].

Most of our patients identified themselves as homosexuals or bisexuals and most of them (61.9%) reported more than 10 sexual partners of the same sex during their lifetime. Sexual behavior apparently contributed to the high frequency of HPV-mediated anal lesions in this group. These behaviors are among the main risk factors for acquisition of co-infection, namely receptive anal intercourse and a large number of sexual partners [11,20,24-27]; this is the main route of transmission

of HPV and HIV [3,24,25] and is an important risk factor for AIN [3,4,28-30].

Surprisingly, 19% of the patients with an abnormal anal examination were heterosexuals. Piketty et al. and Frazer et al. also found that HPV infection and AIN can be acquired by individuals with HIV infection, even without receptive anal intercourse [24,31]. Among the heterosexuals who have not practiced anal intercourse, immunological instability caused by the HIV infection seems to be an important risk factor for the development of anal infection by HPV and AIN [9,24,31,32].

Anoscopy under colposcopic vision proved to be of fundamental importance for detecting and identifying anal lesions and for determining the site of anal biopsy. Anoscopy is known for its role in the elucidation of abnormal cytology findings. All abnormalities detected with anoscopy should be biopsied [1,10,33]. We used the same cervical colposcopy technique as these previous studies. The anosopic examination evaluated the rectal glandular epithelium, the squamous columnar joints, which are the site of most lesions, as well as the anal squamous epithelium. This exam also evaluated the perianal region. The main difficulty with this examination was management of the equipment. Every centimeter of the anorectal mucosa was evaluated through slow removal of the anoscope and repeated adjustment of the colposcopic focus when the acetic acid was applied to each segment of the mucosa. This requires much attention on the part of the examiner and cooperation of the patient.

It is recommended that insertion of the anoscope, and subsequent insertion of the gauze imbibed with acetic acid, be followed by withdrawal of the anoscope; three minutes later the gauze should be removed and the anoscope reinserted [34]. This technique, besides being uncomfortable, due to insertion of the anoscope at two different moments, causes detachment of the anorectal epithelium because of prolonged

Table 3. Diagnosis correspondence among anoscopy under colposcopic vision, anal cytology and anal biopsy.

Anoscopic findings	Anal cytology						Anal biopsy									
	Normal		LSIL		ASCUS		Refuses		Normal		LD		HD		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Suggestive of low-grade	6	28.6	4	19.0	-	-	1	4.8	3	14.3	2	9.5	4	19.0	10	47.6
Suggestive of high-grade	-	-	2	9.5	2	9.5	1	4.8	-	-	-	-	3	14.3	4	19.0
Condyloma	4	19.0	1	4.8	1	4.8	2	9.5	-	-	3	14.3	1	4.8	6	28.6
Micropapillae	1	4.8	-	-	-	-	-	-	-	-	1	4.8	-	-	1	4.8
Total	11	52.4	7	33.3	3	14.3	4	19.0	3	14.3	6	28.6	8	38.1	21	100.0

LD=low-grade (atypical related to infection by HPV, condylomata and AIN 1); HD=high-grade (AIN 2, PAIN 2 and AIN 3).

action of acetic acid; this makes evaluation difficult and distorts the limits between these layers of epithelium.

Although many studies indicate anal cytology as the principal examination technique for screening high-risk groups for AIN and anal cancer, its effectiveness is not well established [33-36]. Reported sensibility ranges between 69% and 93%, with a specificity of between 32% and 59% [33-36]. These variations may be due to the methods used in the collection of anal specimens, the type of cytology technique employed or inter- and intra-observer variation between pathologists [10,32,33]. Anal cytology exams of our group of patients evidenced abnormalities in just 47.6% of the individuals with a lesion at anoscopy, and no HSIL was observed with cytology. The prevalence of abnormal cytology in HIV-positive men varies; whereas Moscicki et al. and Wilkin et al. found prevalence rates of 41.2% [9] and 48% [21], similar to what we found, Sirena et al. reported 75% abnormal cytologies [30].

The anosopic findings correlated well with the biopsy results; in all the patients with anosopic findings suggestive of high-grade lesions, this diagnosis was confirmed at histology. The main abnormalities associated with high-grade lesions in our patient group were dense acetowhite epithelium associated with thick punctuation or mosaic patterns. A previous study had similar findings; vascular alterations, such as punctuation and mosaics, were more frequently associated with high-grade AIN, while micropapillae and condylomata were more associated with low-grade AIN; a mosaic pattern was uncommon in low-grade lesions [12].

In a study of 186 anal biopsies of HIV-positive patients, among the 103 lesions with indication of an anal lesion < HSIL at anoscopy, 60 actually corresponded to a biopsy < AIN 2. Among the remaining 83 anosopic findings suggestive of a lesion ≥ HSIL, 62 corresponded to a lesion ≥ AIN 2 at biopsy [37].

This study also showed that condylomata lesions are associated with both low-grade and high-grade lesions on histology, demonstrating the fundamental importance of investigating any abnormal anosopic finding. Jay found that among anosopic findings suggestive of condyloma, 91% were really low-grade lesions at biopsy and 8% high-grade AIN [12]. These findings reinforce the importance of investigating condylomas, because they may hide a higher-grade lesion [10,12].

We found only a moderate degree of correspondence between the results of cytology and those of the histological examinations. Cytology showed alterations of lower intensity than those observed in the biopsies. Other authors also reported disagreement between cytology and biopsy results [4,8]. Arain et al. found an agreement of 90% between a diagnosis of HSIL and a high-grade AIN; however, when there was cytologic diagnosis of ASCUS and LSIL, there was only a 46%-56% likelihood of a high-grade AIN on biopsy [8]. Sanjose et al. reported that cytologic diagnosis of ASCUS is more frequently associated with AIN detection on biopsy and with anosopic abnormalities [4]. The rate of discrepancy is high when compared with cervical cytology, in which ASCUS and LSIL are associated with a 5%-17% likelihood of being a high-grade AIN on biopsy [38,39].

Lacey et al. also demonstrated that anal cytology tends to underestimate the grade of the lesion; the sensibility of anal cytology to detect an HSIL, which corresponds to a high-grade AIN on biopsy, is around 78% [40]. However, Palefsky et al. found that the sensibility of cytology increased when it is carried out periodically in HIV-positive patients [34]. Likewise, Chin-Hong & Palefsky have shown that the sensibility of anal cytology is greater in HIV-positive men, when compared with HIV-negative men, probably because HPV-mediated anal lesions are more common in this risk group [1].

Conclusions

Discrepancies were observed between the results of the three methods of examinations used in the diagnosis of HPV-mediated anal lesions, especially for cytology, which underestimated the frequency and the grade of the lesions. These findings reinforce the importance of anoscopy under colposcopic vision for the detection of lesions and for determining the site of a biopsy. Considering that patients have few if any symptoms, routine use of these diagnostic methods is important for the prevention of anal squamous cancer in individuals with HIV/AIDS.

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