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THE VALUE OF HIGH-RESOLUTION ANOSCOPY IN THE DIAGNOSIS OF ANAL CANCER PRECURSOR LESIONS IN HIV-POSITIVE PATIENTS

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ABSTRACT – ***Context*** – Anal cancer, although a still rare disease, is being observed in ascending rates among some population segments known to be at risk for the development of the disease. Human papillomavirus (HPV) infection, immunodepression and anal intercourse are some factors associated with the development of the malignancy. Its similarities to cervical cancer have led to many studies aiming to establish guidelines for detecting and treating precursor lesions of anal cancer, with the goal of prevention. High-resolution anoscopy is routinely used for the diagnosis of anal cancer precursor lesions in many centers but the medical literature is still deficient concerning the role of this diagnostic modality. ***Objectives*** - To evaluate diagnostic validation and precision measures of high-resolution anoscopy in comparison to histopathological results of anal biopsies performed in HIV-positive patients treated at the Tropical Medicine Foundation of Amazonas, AM, Brazil. To observe any possible association between some risk factors for the development of anal cancer and the presence of anal squamous intraepithelial lesions. ***Methods*** – A hundred and twenty-eight HIV-positive patients were submitted to anal canal cytological sampling for the detection of HPV infection by a PCR based method. High-resolution anoscopy was then performed after topical application of acetic acid 3% in the anal canal for 2 minutes. Eventual acetowhite lesions that were detected were recorded in respect to location, and classified by their tinctorial pattern, distribution aspect, relief, surface and vascular pattern. Biopsies of acetowhite lesions were performed under local anesthesia and the specimens sent to histopathological analysis. The patients were interviewed for the presence of anal cancer risk factors. ***Results*** - The prevalences of anal HPV infection and of anal squamous intraepithelial lesions in the studied population were, respectively, 79% and 39.1%. High-resolution anoscopy showed sensibility of 90%, specificity of 19.23%, positive predictive value of 41.67%, negative predictive value of 75%, and a kappa coefficient of 0.076. From the analyzed lesions, high-grade squamous intraepithelial lesions was more frequently observed in association to dense (68%), flat (61%), smooth (61%), non-papillary (83%) and normal vascular pattern (70%) acetowhite lesions, while low-grade squamous intraepithelial lesions tended to be associated to dense (66%), flat-raised or raised (68%), granular (59%), non-papillary (62%) and normal vascular pattern (53%) acetowhite lesions. No statistical significance was observed as to the association of epidemiological characteristics and of most of the investigated anal cancer risk factors and presence of acetowhite lesions or anal squamous intraepithelial lesions. However, anal receptive sex and anal HPV infection were significantly associated to anal squamous intraepithelial lesions ($P = 0.0493$ and $P = 0.006$, respectively). ***Conclusion*** - High-resolution anoscopy demonstrated to be a sensitive, but not specific test for the detection of anal squamous intraepithelial lesions. Risk factors anal receptive sex and anal HPV infection were significantly associated to the presence of anal squamous intraepithelial lesions. Based on high-resolution anoscopy image data, acetowhite lesions relief and surface pattern were prone to distinguish between low-grade squamous intraepithelial lesions and high-grade squamous intraepithelial lesions.

HEADINGS – Anus neoplasms. HIV. Papillomavirus infection. Proctoscopy.

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INTRODUCTION

Anal cancer has a low incidence corresponding to 1.5% of all tumors detected in the digestive tract in the United States[42]. In Brazil, according to the National Institute of Cancer (INCA), the incidence of anal cancer is reported in association to the incidence of colorectal cancer. In 2009, 4.24 men/100,000 and 4.44 women/100,000 were reported to have colorectal cancer in the state of Amazonas. This type of cancer is ranked as the 4th most detected type in Brazil, and 6th in the north of Brazil[4].

The number of new cases of cancer has significantly increased in distinct groups of population, defined as groups at risk to develop the malignancy[28]. They are composed of either immune compromised individuals or individuals engaged in recognized risky activities, namely participation in anal receptive intercourse (especially males)[9, 10, 33, 40], immunosuppressed transplanted patients[36], individuals with a history of sexually transmitted diseases (STD)[5, 24, 25,30], women presenting a history of cervical cancer or of cervical, vulvar or vaginal squamous intraepithelial lesions[10], individuals with chronic anal inflammation due to fistulas, fissures and hemorrhoids[40], tobacco smokers[16], and individuals with anal cancer due to genetic factors[14].

Among STD, the human papillomavirus (HPV) is well known for causing epithelial proliferative lesions and, based on its oncogenic potential, to evolve into benign warts or high-grade lesions that can turn to skin and mucous malignant tumors[31, 50].

HPV infection and development of precursor lesions of cervical cancer generally occur in the transformation zone (squamocolumnar junction) of the uterine cervix. Similarly, the anal transitional zone corresponds to the junction of the anal stratified squamous epithelium to the glandular epithelium of the rectum[27], an area where HPV infects cells of the basal layer of the epithelium through micro lesions[12]. Cell and tissue atypical changes in the anogenital area are called anal squamous intraepithelial lesions (ASIL), which, according to the oncogenic potential of the resident HPV type, may or may not evolve into anal cancer[45].

The incidence in the number of cases of cervical cancer has been reduced from 40/100,000 to 8/100,000 in countries where cervical cancer precursor lesions are routinely monitored[41]. Based on similarity between ASIL and cervical precursor lesions, a similar routine has been proposed for diagnosing pre-cancerous anal lesions[29]. Consequently, a cytology test equivalent to the Pap smear to diagnose cervical cancer is also used to diagnose anal lesions. However, even though this test is efficient, inexpensive[44] and highly sensitive (98%) to detect cellular alterations, it has low specificity (50%)[37]. So in cases of anal cell changes with signs of dysplasia of any magnitude, tend to indicate the use of anuscopy with magnified a procedure similar to cervical[8, 23].

In this example, it is observed, with special attention, the squamocolumnar transition zone after topical application of acetic acid 3%, lesions suspected to be produced by the cytopathic effect of HPV will become whitish and underwent biopsy[26]. The histopathological result of a high resolution anoscopy (HRA) monitored biopsy is considered the gold-standard test for confirming the presence of an anal squamous intraepithelial lesion[35, 43].

However, even though HRA is a tool routinely used in the diagnosis of anal lesions, there is little information in the medical literature regarding the success of this medical diagnostic technique regarding the detection of anal cancer precursor lesions.

This study was designed to investigate the importance of high-resolution anoscopy as a diagnostic tool to recognize anal lesions associated to ASIL, in order to validate its utilization in the continuous monitoring program of HIV-positive patients treated at Tropical Medicine Foundation of Amazonas (FMT-AM), Manaus, AM, Brazil, a population sub-group that has a well-known high potential to develop anal cancer precursor lesions. The research will also evaluate in the population sample treated at the institution: 1) the association among the presence of risk factors for the development of anal cancer and the findings of acetowhite lesions (AWL) at HRA and of ASIL at histopathological analyses; 2) the association between the histopathological results that followed HRA monitored biopsies and the presence of HPV anal infection, according to PCR analysis; and 3) the prevalence of ASIL and HPV infection in the studied population.

METHODS

After approval at the Ethics in Research Committee of FMT-AM, a primary transversal descriptive diagnostic study was performed in 128 HIV-positive patients of both genders seen in the coloproctology outpatient clinic of the institution. All the patients signed an informed consent agreement.

After anal canal cytological sampling for the performance of a PCR based HPV detection test according to the method described by Bauer and Manos[2], patients were submitted to HRA, by three colorectal surgeons (FSG, ITCS, AGDPG), after topical application of 3% acetic acid, in the anal canal, for 2 minutes. Observed AWL had their location, tinctorial characteristics (acetowhite negative, tenuous or dense), aspect (focal or coalescent), relief (flat, slightly elevated, or elevated lesions), surface (smooth or granular; papillary or nonpapillary), as well as vascular profile (normal or atypical; warty vessels or no warty vessels, punctation or no punctation, mosaicism or no mosaicism) documented according to a modified version of the Barcelona classification (2002)[49]. Biopsies of AWL were performed for histopathological analysis under local anesthesia. When no AWL was observed, biopsies were performed in a standardized location (just above the pectinate line at the 7 o'clock position, considering 12 o'clock the anterior commissure).

The histopathological results of the anal biopsies were classified as: negative (including benign inflammatory alterations), low-grade squamous intraepithelial lesions (LSIL, including anal condyloma) or high-grade squamous intraepithelial lesions (HSIL)[3].

The criteria investigated to define groups at risk to develop anal cancer were as follows: report of anal receptive intercourse, number of sexual partners in the last 5 years, age at which individuals became sexually active, actual and past patient information for STD, HPV infection status, T CD4+ lymphocyte levels below 200 cell/μL, use of antiretroviral therapy (HAART), presence of benign concomitant diseases, history of smoking and of drug addiction.

Data were evaluated in contingency tables in which values were statistically analyzed by Pearson's chi-square test or Fisher's exact test. Independent variables such as age were analyzed by the Mann-Whitney U test. Agreement between the presence of AWL at HRA and the histopathological diagnosis of ASIL was evaluated by kappa statistics interpreted according to Landis and Koch criteria (<0.00 = poor; 0.00 – 0.20 = weak; 0.21 – 0.40 = regular; 0.41 – 0.60 = moderate; 0.61 – 0.80 = strong; 0.81 – 1.00 = almost perfect).

Significance level values of 0.05 and confidence intervals of 95% were established for all analysis.

RESULTS

Table 1 shows the distribution of HIV-positive patients as to receptive anal sex, number of sexual partners in the last 5 years, onset of sexual activity, presence or history of STD and HPV infection in relation to the presence of ACW lesions and ASIL.

Table 2 correlates CD4 cells counts, use of highly-active antiretroviral therapy, presence of concomitant benign diseases, smoking and illicit drug addiction with the presence of ACW lesions and ASIL in HIV-positive patients.

Table 3 depicts the diagnostic validation and precision measures of high-resolution anoscopy obtained in this study in comparison to the gold-standard histopathology.

Table 4 denotes the phenotypic characteristics of HRA of HIV-positive patients, relative to the results of the histopathological analyses of the anal biopsies performed after topical application of 3% acetic acid.

Table 5 correlates the results of PCR for HPV and histopathological results of anal biopsies performed in HIV-positive patients.

Figures 1 to 6 depict phenotypic HRA characteristics of AWL and indicate their correlation with corresponding PCR for HPV and histopathological findings.

DISCUSSION

Data analysis of factors involved in anal carcinogenesis

Acetowhite lesion

No statistical significance was observed in the correlation between risk factors for anal cancer and the occurrence of AWL (P>0.05) (Tables 1 and 2).

Intraepithelial lesions

Nevertheless, of 89 patients participating in anal intercourse, 40 presented ASIL (44.94%) at anal biopsies, while only 10

TABLE 1. Distribution of HIV-positive patients, individuals participating in anal receptive intercourse, number of partners in the last 5 years, age at which individuals became sexually active, actual and past patient information for STD, HPV infection information regarding presence of squamous intraepithelial lesions

Variable	Acetowhite lesions				Total	*P*-value*	Anal intraepithelial lesion				Total	*P*-value*
	Positive		Negative				Positive		Negative			
	n	%	n	%			n	%	n	%		
Anal intercourse						0.6083*						0.0493*
Yes	76	85.39	13	14.61	89		40	44.94	49	55.06	89	
No	32	82.05	7	17.95	39		10	25.64	29	74.36	39	
Nr sexual partners last 5 years						0.7632*						0.3806*
≤ 10	80	83.33	16	16.67	96		35	36.46	61	63.54	96	
> 10	24	88.89	3	11.11	27		13	48.15	14	51.85	27	
Sexual activity initiation						0.128*						0.1688*
≤ 14 years-old	35	76.09	11	23.91	46		14	30.43	32	69.57	46	
> 14 years-old	67	88.16	9	11.84	76		34	44.74	42	55.26	76	
History of STD						0.647*						0.9547*
Yes	60	85.71	10	14.29	70		27	38.57	43	61.43	70	
No	48	82.76	10	17.24	58		23	30.66	35	60.34	58	
History of HPV						0.241*						0.006*
Yes	88	86.27	14	13.73	102		46	45.10	56	54.90	102	
No	20	76.92	6	23.08	26		4	15.38	22	84.62	26	

Value in bold indicates *P*-value with statistical difference at the 5% level

* Pearson's chi-square test or Fisher's exact test

TABLE 2. Distribution of HIV-positive patients according to T-CD4 cell counts, use of highly active anti-retroviral therapy (HAART), presence of concomitant benign anal diseases, smoking, drug addiction in correlation to high-resolution anoscopy and histopathological findings.

Variable	Acetowhite lesions				Total	*P*-value*	Anal intraepithelial lesion				Total	*P*-value*
	Positive		Negative				Positive		Negative			
	n	%	n	%			n	%	n	%		
T-CD4 count						0.26*						0.06*
< 200/µl	26	78.78	7	21.21	33		8	24.24	25	75.76	33	
≥ 200/µl	76	87.35	11	12.64	87		38	43.68	49	56.32	87	
HAART						0.8423*						0.3134*
Yes	49	85.96	8	14.04	57		19	33.33	38	66.67	57	
No	59	83.10	12	16.90	71		31	43.66	40	56.34	71	
Benign anal diseases						0.3215*						0.8845*
Yes	92	85.98	15	14.02	107		42	39.25	65	60.75	107	
No	16	76.19	5	23.81	21		8	38.10	13	61.90	21	
Smoking						0.3146*						0.513*
Yes	38	79.17	10	20.83	48		17	35.42	31	64.58	48	
No	70	87.50	10	12.50	80		33	41.25	47	58.75	80	
Drug addiction						0.5077*						0.8053*
Yes	22	78.57	6	21.43	28		12	42.86	16	57.15	28	
No	86	86	14	14	100		38	38	62	62	100	

Value in bold indicates *P*-value with statistical difference at the 5% level
* Pearson's chi-square test or Fisher's exact test

TABLE 3. Diagnostic efficiency of high resolution anoscopy

HRA/Pathology	ASIL+*	ASIL-*	Total
AWL+*	45	63	108
AWL-*	5	15	20
Total	50	78	128

*AWL+ = positive acetowhite lesions;
AWL- = negative acetowhite lesions.
ASIL+ = positive histopathology;
ASIL- = negative histopathology.
Accuracy = 46.87%
Sensitivity = 90%
Specificity = 19.23%
Positive predictive value = 41.67%
Negative predictive value = 75%
False positive = 89.76%
False negative = 10%
ASIL prevalence = 39.1%
Chi-square test *P* = 0.2142
Kappa test = 0.076

(25.64%) of those who did not mention anal intercourse activity had the same diagnosis ($P = 0.04930$) (Table 1). Palefsky et al.[29] observed a relationship between ASIL and anal receptive sex in HIV-positive patients. They reported that 50% of HIV-positive men-who-have-sex-with-men (MSM) in their study presented ASIL. Fox et al.[13] reported ASIL was found in HIV-positive MSM in a prevalence of 26% and 36% in two cohort studies undertaken at the USA mainly before the advent of HAART. Gimenez et al.[18] have previously reported a prevalence of ASIL in HIV-positive MSM of 42% ($P = 0.03$).

Regarding the number of sexual partners in the last 5 years, there was no statistical significance in the correlation with histopathological diagnoses of ASIL of any grade. Thirty-five (36.46%) individuals who reported having less than 10 partners presented ASIL, while 13 (48.15%) of those that had more than 10 partners also presented the same histopathological finding (Table 1). These results are inconsistent with a study by Frisch et al.[15] in which it was observed that more than 10 sexual partners increased the risk of cancer by 5 times in women and 2.8 times in men. Klencke and Palefsky[22] observed that, in this case, the exposure to various HPV types is the real risk factor to the increasing incidence of ASIL and of anal and cervical cancer observed in these patients.

The average age for first engaging in sexual activity was 14.65 years in the patients studied herein. There was no statistical significance in the correlation between age at which individuals began sexual activity and ASIL. Of 46 patients who began having sex as early as 14 years old, 14 (30.43%) were ASIL positive. Seventy-six individuals started having sex after the age of 14; among those, 34 (44.74%) were ASIL positive (Table 1). In comparison, Frisch et al.[15] observed moderately elevated risk for anal cancer in females who started having sex earlier than 16 years old in comparison to women who first had sexual intercourse after the age of 20 years.

Seventy patients reported an actual or past history of STD; among these, 27 (38.57%) presented ASIL. Twenty-three (30.66%) patients with no STD history presented lesions. Therefore, there was no statistical significance between the

TABLE 4. Correlation between image characteristics of high-resolution anoscopy and histopathological results

	Histopathology							
Anoscopy	**Neg**	%	**LSIL**	%	**HSIL**	%	**Total**	***P****
Tinctorial characteristics								**0.005**
Negative AWL	15	75.00	4	20%	1	5%	20	
Dense AWL	28	44.44	22	34.92	13	20.63	63	
Tenuous AWL	35	77.78	6	13.33	4	8.89	45	
Lesion distribution aspect								0.921
Focal	30	56.60	14	26.42	9	16.98	53	
Coalescent	33	60.00	14	25.45	8	14.55	55	
Relief							6	**<0.001**
Flat	49	74.24	6	9.09	11	16.67	66	
Slightly elevated	9	37.50	10	41.67	5	20.83	24	
Elevated	5	27.78	12	66.67	1	5.56	18	
Surface								**0.002**
Smooth	44	68.75	9	14.06	11	17.19	64	
Granular	18	41.86	19	44.19	6	13.95	43	
Papillary	4	21.05	12	63.16	3	15.79	19	**<0.001**
Nonpapillary	74	67.89	20	18.35	15	13.76	109	
Vascular Profile								
Normal	52	63.41	17	20.73	13	15.85	82	0.3631
atypical	6	46.15	5	38.46	2	15.38	13	
warty vessels	3	42.86	3	42.86	1	14.29	7	0.5691
no warty vessels	59	59.00	25	25	16	16	100	
punctation	1	33.33	2	66.67	0	0	3	0.2248
no punctation	62	59.61	26	25	16	15.38	104	
mosaicism	1	50.00	1	50	0	0	2	0.666
no mosaicism	61	58.09	27	25.71	17	16.19	105	

Neg: ASIL negative, including inflammatory alterations, LSIL: low-grade squamous intraepithelial lesion, HSIL: high-grade squamous intraepithelial lesion, AWL: acetowhite lesion

TABLE 5. Correlation between presence of HPV anal infection and anal cancer precursor lesions

PCR/ histopathology	**ASIL+**	%	**ASIL-**	%	**Total**	***P*-value**
HPV+	46	45.10	56	54.90	102	0.006
HPV-	4	15.38	22	84.62	26	
Total	50		78		128	

HPV+: presence of HPV, HPV-: absence of HPV.
ASIL+: presence of anal cancer precursor lesion; ASIL-: absence of anal cancer precursor lesion

two groups (Table 1). Regarding anal cancer, Frisch et al.[15] observed a relationship between STD and anal neoplastic development. In 2002, Frisch[17] reported that most STD related to anal cancer were also associated with HPV infection.

Statistical significance was observed between the presence of anal papillomavirus infection, according to PCR results, and ASIL (P = 0.006). Forty-six HPV positive patients (45.10%) presented ASIL, while only four (15.38%) non-infected patients presented lesions (Table 1). Palefsky et al.[32] observed, back in 1998, that nearly all HIV-positive male patients with lymphocytes T-CD4 counts less than 500/mm³ they were following in the city of San Francisco presented PCR detected anal HPV infection. They also reported that 72% of HIV-positive males with CD4 counts less than 200/mm³ had abnormal anal cytology, so that, taken together, both findings pointed to a probable high prevalence of ASIL in these patients. Indeed, commenting about a work performed by his group in the San Francisco bay to investigate his earlier assumptions and published in 2008, Palefsky states that the prevalence of ASIL of any grade in HIV-positive MSM was

57% (43% HSIL) and that HPV infection was detected in 88% of these patients, 72% of whom were oncogenic HPV[34].

Thirty-three of the patients studied herein presented T-CD4 levels below 200 cells/μL, eight (24.24%) of those were ASIL positive. Among those patients presenting T-CD4 cells counts above 200/μL, 38 (43.68%) were ASIL positive, demonstrating no correlation between T-CD4 levels and ASIL (Table 2). The same was observed in patients who were under HAART. Nineteen patients (33.33%) that received the medication were ASIL positive, while 31 (43.66%) patients who did not use the medication were also positive for ASIL (Table 2). Abramowitz et al.[1] also observed no correlation in the association of levels of T-CD4 lymphocytes, use of HAART and ASIL. On the other hand, Piketty et al.[38] reported a high prevalence of ASIL (64%) in patients using HAART when their immunity was restored and Palefsky[34] described an increase in number of cases of anal and cervical cancer despite the use of HAART.

There was also no statistical significance in the association between ASIL and the presence of anal benign diseases (hemorrhoids, hypertrophied papilla, anal fistula, anal fissure, mucosal prolapse, anal pruritus, and proctitis) in the 107 individuals in whom these characteristics were studied. Among these patients, 42 (39.25%) were positive for ASIL, while 8 of 27 patients (38.10%) who did not present any listed disease were also positive (Table 2). These results are not consistent with the findings of Frisch et al.[14] and Tseng et al.[47] who noticed a significant relation between benign anal lesions and anal cancer, although no case of anal cancer was observed among our patients.

Our data did not find any association of smoking with the presence of ASIL. We observed that among 48 smokers, 17 (35.42%) were positive for ASIL, while 70 (87.50%) non-smokers also presented ASIL (Table 2). Contrarily (considering ASIL a stage of anal cancer development), Tseng at al.[47] reported an association between smoking and anal cancer and Daling et al.[11] showed that smoking was associated with an odds ratio of 3.9 to develop anal cancer.

There was no statistical significance between the presence of ASIL and addiction to hallucinogen drugs. Among drug users, 42.86% presented intraephitelial lesions, while 38% of non-drug users also presented ASIL (Table 2). In contrast, Ching-hong et al.[6] reported statistical significance for this factor ($P = 0.03$), while Piketty et al.[37] reported 34% of cases of ASIL in HPV positive heterosexual individuals using drugs.

Diagnostic accuracy of HRA

HRA was associated with high sensitivity (90%) but low specificity (19.23%) for the diagnosis of ASIL, with a negative predictive value of 75% and a low positive predictive value of 41.67% (Table 3). False positive and false negative rates were, respectively, 89.76% and 10%. Sensitivity and specificity rates of HRA vary greatly in the literature, since this is still a very subjective, as well as user, equipment and other-comorbidity-dependent test[7, 19, 26, 46]. Values vary from 59%[26] to 100%[46] for sensitivity and from 66%[46] to 74%[24] for specificity. However, more concordantly with our results, Tuon et al.[48] reported for cervical colposcopy, a much more widely employed and studied method, a specificity rate as low as 19%.

Correlating the presence of AWL with the histopathological diagnosis of ASIL, there was no statistical significance between the variables according to the chi-square test (0.2142), whereas the kappa test (0.076) showed low evidence of agreement between the variables. This is possibly a consequence of the fact that lesions such as hypertrophied papillae, hemorrhoids and inflammation in anal canal used to stain positively by acetic acid, a reflection of the 63 acetowhite-positive lesions that were negative for ASIL, as well as due to HRA interpretative differences among three individual observers.

Diagnostic agreement between HRA images and histopathology

Regarding tinctorial quality of HRA a significant relationship was observed relative to the presence of histopathologically confirmed ASIL ($P = 0.005$), for of 20 patients with HRA negative for AWL, 15 (75%) had negative histopathological results, 4 (20%) presented LSIL and 1 (5%) HSIL. Likewise, regarding dense AWL, 28 (44.44%) of 63 patients had negative histopathological results, 22 (34.92%) presented LSIL and 13 (20.63%) HSIL. On the other hand, of 45 individuals with tenuous AWL, 35 (77.78%) had negative histopathological results, 6 (13.33%) presented LSIL and 4 (8.89%) HSIL. A proportion of HSIL (72%) and LSIL (69%) lesions were described as dense AWL. Based on the odds ratio, dense AWL were 2.3 times more likely to be an HSIL than a tenuous lesion (21% of dense AWL lesions were HSIL compared to 9% of tenuous AWL lesions). But, accordingly, a dense AWL was 2.7 times more likely to be an LSIL than a tenuous lesion.

Regarding the relief of lesions observed at HRA, flat lesions tended to be mainly negative for ASIL, but HSIL lesions were more frequently flat at HRA than LSIL. While slightly elevated lesions were more often either negative for ASIL or LSIL, elevated lesions tended to be LSIL. These results showed statistical significance ($P<0.001$). HSIL lesions tended to be significantly more associated to flat AWL than LSIL ($P<0.001$). A high-grade lesion was 3 times more prone to be flat than to be elevated (16% of flat lesions were HSIL compared to 5% of elevated lesions). Comparatively, Jay et al.[21] observed that flat lesions were 4 times more frequently associated to HSIL than elevated lesions (39% of flat lesions were HSIL compared to 9% of elevated lesions).

When surface aspect was analyzed, smooth lesions were more frequently observed in relation to negative histopathological results, whereas a granular aspect was not prone to be HSIL and a papillary aspect was more frequently associated to low-grade lesions ($P = 0.002$). Among lesions described as smooth, the probability of them being HSIL were 1.2 times higher than being LSIL (17% of HSIL lesions were smoothv compared to 14% of granular lesions). Jay et al.[21] found that smooth lesions were 2 times more likely to be HSIL than granular lesions

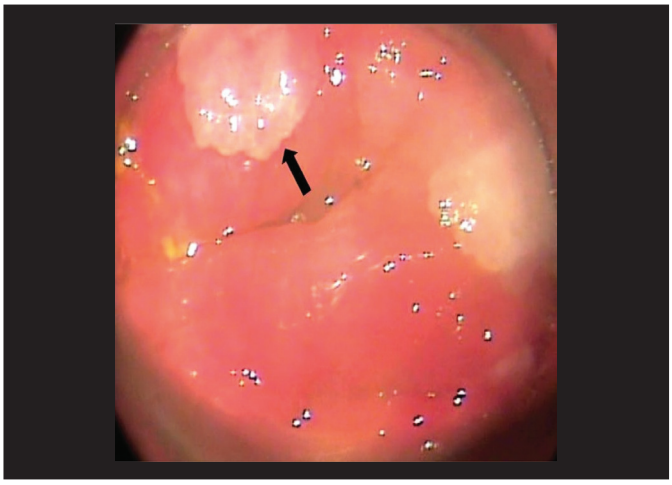

FIGURE 1. Positive acetowhile lesion, dense, focal, flat, smooth, non-papillary, HPV positive. Histopathology: HSIL

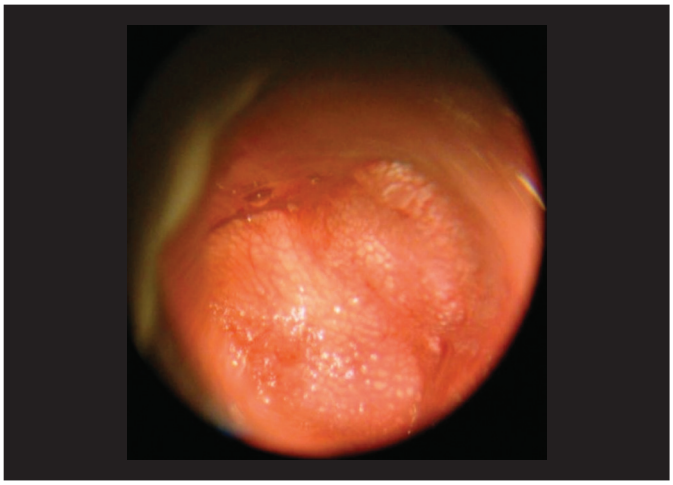

FIGURE 4. Mosaicism, HPV positive. Histopathology: LSIL

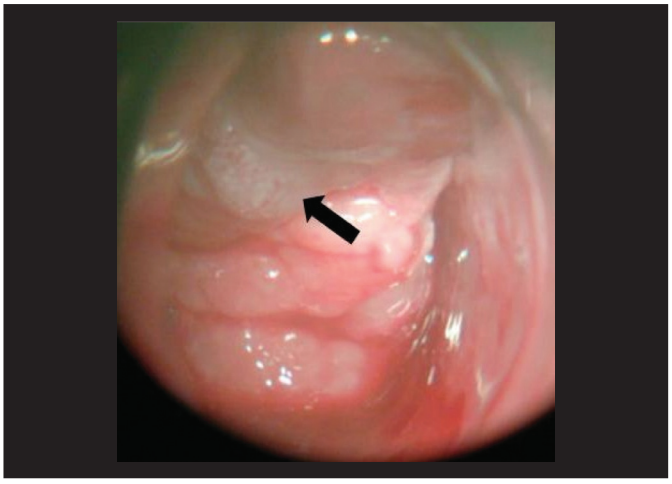

FIGURE 2. Acetowhite lesion dense, coalescent, slightly elevated, papillary, HPV positive. Histopathology: HSIL

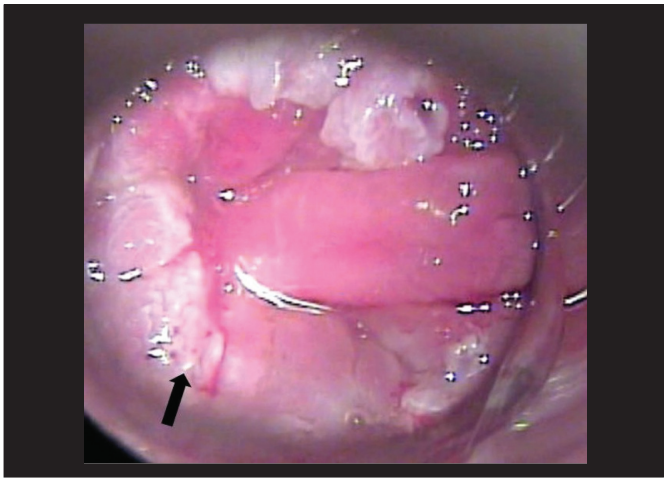

FIGURE 5. Acetowhite lesion dense, coalescent, elevated, granular, punctation, HPV positive. Histopathology: condiloma

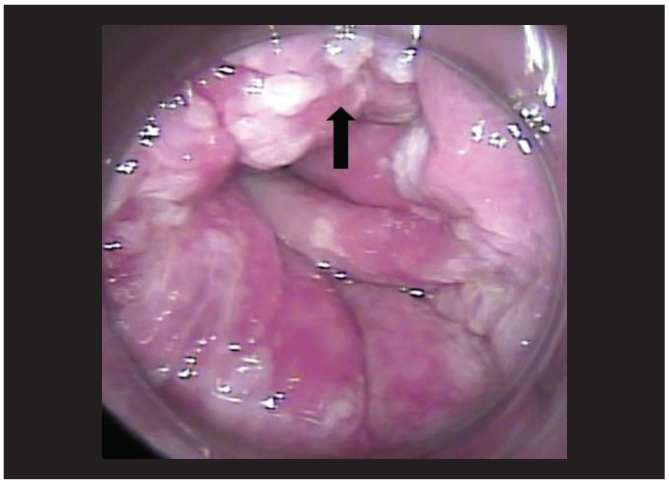

FIGURE 3. Acetowhite lesion, dense, coalescent, slightly elevated, papillary, HPV positive. Histopathology: LSIL

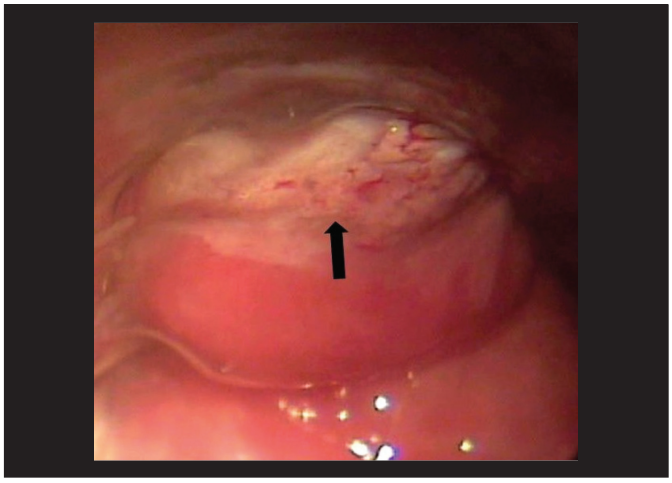

FIGURE 6. Acetowhite lesion dense, slightly elevated, granular, HPV positive. Histopathology: LSIL

(31% of smooth lesions were HSIL compared to 13% of granular lesions).

Regarding the description of lesions being either papillary or non-papillary, a higher proportion of HSIL (83%) than LSIL (62%) was described as non-papillary (P = 0.001). Non-papillary lesions had a 0.87 times greater chance to be associated to HSIL than LSIL. Jay et al.[21] reported that non-papillary lesions were twice as likely to be HSIL than papillary lesions (34% of non-papillary lesions were HSIL compared to 14% of papillary lesions).

There was no statistical significance for the remaining studied aspects of the lesions and their vascular pattern (Table 4), which is not consistent with the findings of Jay et al.[21], in which warty vessels, punctation and mosaicism all presented a statistical significance at the level of 0.001.

Our data indicate that of the HSIL lesions analyzed 68% were dense AWL, 61% were flat, 61% were smooth, 83% were non-papillary and 70% presented a normal vascular pattern. Regarding LSIL lesions, 66% of them were dense AWL, 68% were slightly elevated or elevated, 59% were granular, 62% were non-papillary and 53% presented normal vascular pattern.

ASIL prevalence

Fifty patients were diagnosed as having ASIL (39.1%) at histopathology: 32 (25%) presented low grade lesions and 18 (14.1%) presented high-grade lesions. These results are similar to other findings in the literature for the prevalence of ASIL, where LSIL ranges from 35.7%[20] to 42%[38], while HSIL from 7.1%[18] to 26%[21].

HPV prevalence

The observed HPV prevalence in the HIV-positive patients studied was of 79%. Other similar findings in the literature present prevalence from 80%[38] to 98%[39].

Correlation between anal cancer precursor lesions and HPV infection

Among 50 patients presenting ASIL, 46 were HPV positive, consistent with a 92% prevalence. Among 32 patients who had LSIL, 30 (93.75%) were HPV positive, while of 18 patients with HSIL, 16 (88.88%) had HPV infection. In a systematic review, 1,824 patients were studied, including 472 and 360 presenting HSIL and LSIL, respectively. The prevalence of HPV in patients presenting HSIL and LSIL was 71.91% and 88%, respectively[20]. Based on the data presented in Table 5, a prevalence of 45% of ASIL was observed HIV-positive patients co-infected with HPV.

CONCLUSIONS

HRA was a highly sensitive method for the detection of ASIL considering the tinctorial quality, relief and surface aspect of AWL which enhanced the capability of distinction between high- and low-grade anal squamous lesions. Nevertheless, due to its poor observed specificity a complementary histopathological study is mandatory in order not to miss unsuspected atypical lesions. The prevalence of anal HPV infection and of ASIL in the studied HIV-positive patients was of, respectively, 79% and 39.1% (25% LSIL and 14.1% HSIL). Anal intercourse and anal HPV infection were highly correlated with the presence of ASIL.

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Gimenez F, Costa-e-Silva IT, Daumas A, Araújo J, Medeiros SG, Ferreira L. Anuscopia de alta resolução: valor diagnóstico em lesões precursoras de câncer anal em pacientes soropositivos.. Arq Gastroenterol. 2011;48(2):136-45.

RESUMO – ***Contexto –*** O câncer anal, muito embora ainda seja uma doença rara, vem sendo observado com frequência ascendente em alguns grupos populacionais considerados sob risco para o desenvolvimento da doença. Infecção pelo vírus do papiloma humano (HPV), imunossupressão e o sexo anoreceptivo são alguns dos fatores associados ao desenvolvimento da neoplasia. Suas semelhanças com o câncer do colo do útero levaram muitos estudos voltados para o estabelecimento de regras para a detecção e tratamento de lesões precursoras do câncer anal, tudo com o objetivo de prevenir a doença. A anuscopia com magnificação de imagem é rotineiramente utilizada para o diagnóstico de lesões precursoras do câncer anal em muitos centros, mas a literatura médica ainda é escassa a respeito do papel a ser desempenhado por essa modalidade diagnóstica. ***Objetivos –*** Avaliar as medidas de validação e precisão diagnósticas da anuscopia com magnificação de imagem em comparação com resultados histopatológicos de biopsias anais realizadas em pacientes HIV-positivos tratados na Fundação de Medicina Tropical do Amazonas, Manaus, AM, Brasil. Observar qualquer possível associação entre alguns fatores de risco para o desenvolvimento do câncer anal e a presença de lesões intraepiteliais escamosas anais. ***Métodos –*** Cento e vinte e oito pacientes HIV-positivos foram submetidos a coleta de material celular anal para a realização da detecção da presença de HPV pela reação em cadeia da polimerase. Anuscopias com magnificação de imagem foram realizadas após a aplicação tópica de ácido acético a 3% no canal anal por 2 minutos. As lesões acetobrancas eventualmente observadas foram registradas com respeito a sua localização e classificadas quanto ao seu padrão tintorial, aspecto de distribuição, relevo, características de sua superfície e vascularidade. Foram realizadas biopsias das lesões acetobrancas sob anestesia local e os espécimes foram remetidos para estudo histopatológico. Os pacientes foram entrevistados em relação à presença de fatores de risco para o câncer anal. ***Resultados –*** As prevalências de infecção anal pelo HPV e de lesões intraepiteliais escamosas anais na amostra populacional estudada foram de 79% e 39,1%, respectivamente. A sensibilidade e a especificidade da anuscopia com magnificação de imagem foram, respectivamente, de 90% e 19,23%, enquanto que o valor preditivo positivo foi de 41,67%, o valor preditivo negativo foi de 75% e o coeficiente kappa de 0,076. Com respeito às lesões analisadas de alto grau foram mais frequentemente observadas em associação com lesões acetobrancas densas (68%), planas (61%), lisas (61%), não-papilíferas (83%) e com padrão vascular normal (70%), enquanto que lesões de baixo-grau tenderam a se associar a lesões aetobrancas densas (66%), plano-elevadas ou elevadas (68%), granulares (59%), não-papilíferas (62%) e de padrão vascular normal (53%). Não se observou significância estatística na associação entre características epidemiológicas e a maioria dos fatores de risco para o câncer anal e a presença de lesão acetobrancas ou de lesões intraepiteliais escamosas anais. Entretanto, o sexo anorreceptivo e a detecção de infecção anal por HPV, segundo a técnica da reação da cadeia de polimerase, associaram-se significantemente com lesões intraepiteliais escamosas anais (P = 0,0493 e P =0,006, respectivamente). ***Conclusões*** – A anuscopia com magnificação de imagem demonstrou ser um método diagnostico sensível, mas inespecífico para a detecção de lesões intraepiteliais escamosas anais. Os fatores de risco sexo anorreceptivo e infecção anal pelo HPV associaram-se significantemente à presença de lesões intraepiteliais escamosas anais. Com base nos achados da anuscopia com magnificação de imagem, o relevo e o aspecto morfológico da distribuição das lesões acetobrancas na superfície do canal anal tenderam a permitir a distinção entre lesões de baixo e alto grau.

DESCRITORES – Neoplasias do ânus. HIV. Infecções por papilomavírus. Proctoscopia.

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