Anal Intraepithelial Lesions in Women With Human Papillomavirus–Related Disease

Silvio Tatti, MD, Veronica Suzuki, MD, Laura Fleider, MD, Veronica Maldonado, MD, Ricardo Caruso, MD, and Maria de los Angeles Tinnirello, MD

Lower Genital Tract and Colposcopic Unit, Hospital de Clinicas "José de San Martín," University of Buenos Aires, Argentina

■ **Abstract**

Objective. This study aimed to determine the prevalence of anal intraepithelial lesions in women with histologic diagnosis of intraepithelial lesions of the lower genital tract.

Materials and Methods. This was a cross-sectional study conducted at the Lower Genital Tract and Colposcopy Unit of Hospital de Clínicas ''José de San Martín,'' University of Buenos Aires, Argentina. A total of 481 women with histologically confirmed low-grade and high-grade cervical, vaginal, or vulvar intraepithelial lesions were evaluated between 2005 and 2011. They were referred for cytologic samples and examination with high-resolution anoscopy. We obtained biopsy specimens of any suspicious colposcopic images.

Results. Of a total of 481 patients, 404 (84%) were immunocompetent, 31 (6.4%) were HIV+, and 46 (9.6%) had other causes of immunosuppression. Moreover, of the 481 patients, 134 (27.86%) had anal intraepithelial neoplasia (AIN); 28 (5.82%) had high-grade AIN and 106 (22%) had low-grade AIN. Women with high-grade cervical intraepithelial neoplasia (CIN 2, 3) had 2 times the odds of developing AIN compared with women with low-grade CIN (CIN 1) (odds ratio = 1.91, 95% confidence interval = 1.1–3.6). Regarding localization, we found statistically significant difference between the frequency of vulvar and anal lesions. Women with vulvar condylomata and vulvar intraepithelial neoplasia (VIN) may be more likely to develop AIN.

Conclusions. Immunocompetent women with CIN, vaginal intraepithelial neoplasia, or VIN may also present high-grade or low-grade anal intraepithelial lesions so we should consider AIN as part of multicentric disease of the lower genital tract. Cervical intraepithelial neoplasia, VIN, condyloma accuminatta, and vaginal intraepithelial neoplasia could be warning signs of anal intraepithelial lesions. ■

Key Words: anal intraepithelial neoplasia, anal neoplasms, human papillomavirus

Anal and cervical cancers have similar biologic, histologic, and epidemiologic characteristics. They are both associated to human papillomavirus (HPV) infection, especially HPV-16. It is believed that anal carcinoma and its precursor lesions behave like cervical lesions. It has been mainly studied in men who have sex with men (MSM) and HIV-positive patients. Non-immunosuppressed women with lower genital tract disease may also have anal intraepithelial neoplasia (AIN). The rate of anal cancer during 2004 to 2008 in the United States among females was 1.8 per 100,000 and 1.2 per 100,000 among males [1]. Anal carcinoma and its precursor lesions have increased in the last decades, especially among MSM, those who had renal transplant [2], and those with other causes of immunosuppression. Women with human immunodeficiency virus (HIV) infection have a higher risk (RR × 6.8) compared with the general population [3, 4]. When highly active anti retroviral therapy was introduced in 1996, the incidence

Reprint requests to: Silvio Tatti, MD, Department of Obstetrics and Gynecology, Hospital de Clínicas ''José de San Martín'' – University of Buenos Aires, 2351 Cordoba Ave (C1120AAF), Ciudad Autónoma de Buenos Aires, Buenos Aires, Argentina. E-mail: colpoclinicas@hotmail.com

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did not reduce [5]. The anal canal and the uterine cervix share common characteristics like their histology, anatomy, and epidemiology [6]. They both have a transformation zone where the squamous and columnar epithelium joins. The mucosa of the anal canal joins the epidermal tissue in the dentate line where we can find more intraepithelial lesions [7]. Cervical cancer has a precursor lesion, high-grade (HG) cervical intraepithelial neoplasia (CIN); anal cancer has an equivalent precursor, HG-AIN, and the same types of high-risk HPV are found in both types of cancers, especially HPV-16 and HPV-18 [8–10].

This study aimed to determine the prevalence of anal intraepithelial lesions in women with histologic diagnosis of intraepithelial lesions of the lower genital tract.

MATERIALS AND METHODS

Study Population

The protocol for the study was approved by the University Hospital's institutional review board. It was a cross-sectional study conducted between September 2005 and July 2011, at the Lower Genital Tract and Colposcopy Unit of Hospital de Clínicas "José de San Martín," University of Buenos Aires, Argentina. Women were eligible for inclusion if they were 18 years or older with histologically confirmed diagnosis of the lower genital tract intraepithelial neoplasia. Women with absence of the rectum, history of anal carcinoma, or pregnancy were excluded. A total of 481 consecutive women accepted to participate. Ten women did not accept to enter the study.

Study Design

At the moment of histologic diagnosis of low-grade and high-grade cervical (CIN), vaginal (VAIN), vulvar (VIN) or perineal (PEIN) intraepithelial neoplasia, or vulvar condylomatta, patients were offered to patients were offered to participate in the present study. All these individuals were referred for cytologic samples and examination with high-resolution anoscopy (HRA) simultaneously at their initial visit. After obtaining written consent, each patient provided a detailed history on routine gynecologic health care and risk behaviors. This assessment by questionnaire included history of anal intercourse, number of sexual partners, history of cigarette smoking, conditions of immunosuppression such us HIV, systemic lupus erythematosus, solid organ transplant, or high-dose systemic steroids.

After the questionnaire and history, we examined the cervical, vulvar, and vaginal regions in dorsolithotomy position. Then, with the patient in left lateral decubitus position, samples for anal cytology were collected. Subsequently, we performed digital rectal examination to palpate any mass or ulcers and to recognize any tender area. After the digital rectal examination, we inserted a disposable anoscope and a gauze that has been soaked in 5% acetic acid. We removed the anoscope, leaving the gauze for 2 minutes in the anal canal. Then we removed the gauze, inserted the anoscope again, and performed the HRA using the colposcope with a 16× to 25× magnification to observe the anal canal, the anal transformation zone, the dentate line, and the margin and perianal skin. We took biopsy with a small biopsy forceps of any suspicious colposcopic images like leukoplakia, suspicious acetowhite changes, mosaicism, punctuation, or irregular vessels (Figures 1–4) using local anesthesia with lidocaine 2% for all biopsies distal to the dentate line and Monsel (i.e., ferric subsulfate) solution for hemostasis. All colposcopy and HRA procedures were performed by a gynecologist with expertise in colposcopy and HRA. All cytologic and histologic samples were analyzed by gynecologic pathologists of the same hospital using the same diagnostic criteria.

Findings from the anal cytology were classified according to the 2001 Bethesda System for cervical cytology, and findings from the histologic samples were classified as normal, low-grade AIN (LG-AIN; i.e., AIN 1) or HG-AIN (i.e., AIN 2, 3).

Statistical Analysis

A total of 481 women with histologically confirmed LG and HG cervical, vaginal, vulvar, or perineal intraepithelial lesions were evaluated between 2005 and 2011.

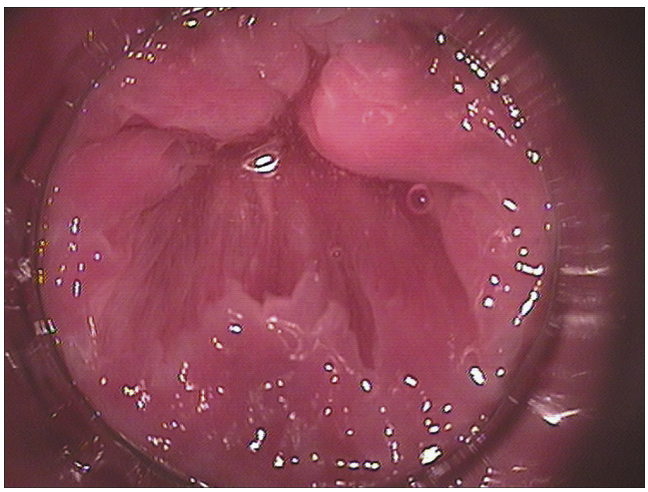

Figure 1. Squamocolumnar junction.

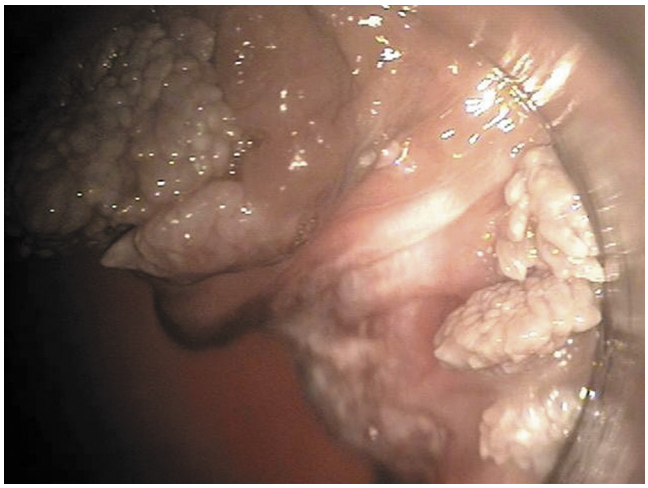

Figure 2. High-resolution anoscopy of intra-anal condylomas.

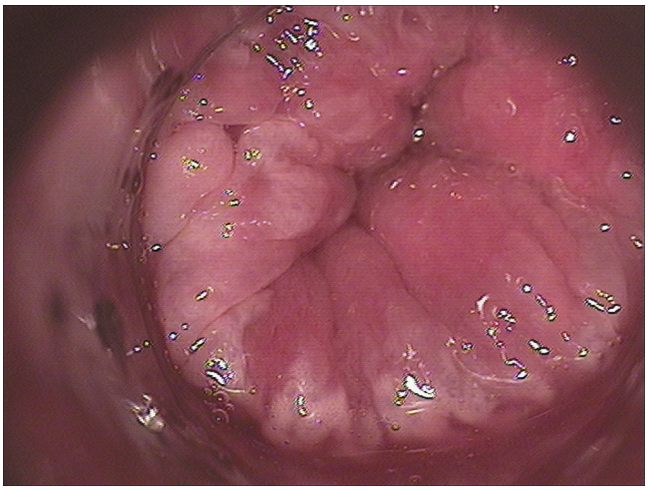

Figure 4. High-resolution anoscopy of HG-AIN.

For the comparison between immunocompetence status and selected variables and for the comparison between results of anal biopsy and selected variables, Student *t* test, χ^2 test, Fisher test, and Wilcoxon rank sum test were used as appropriate. For association between the presence of AIN and other intraepithelial lesion of the lower genital tract, odds ratio was used. A $p < .05$ on a 2-sided test was considered statistically significant. Statistical analysis was performed using SPSS version 15 (SPSS, Inc, Chicago, IL).

RESULTS

A total of 481 women were enrolled in the study between September 2005 and July 2011. Their mean age at enrollment was 35 years (range = 18–83 y). Of the 481 women, 404 (84%) were immunocompetent, 31 (6.4%) had HIV infection, and 46 (9.6%) had other causes of immunosuppression.

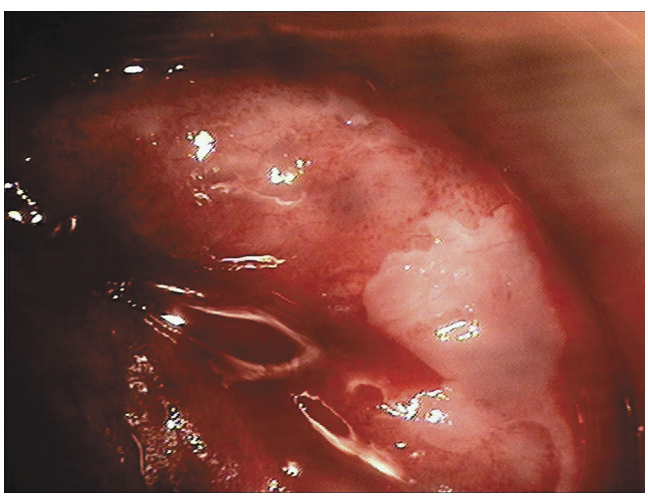

Figure 3. High-resolution anoscopy of HG-AIN.

In the immunocompetent patient group, 28% reported 5 or more lifetime sexual partners and their median age at first sexual intercourse was 17 years. Moreover, 48% reported a history of receptive anal intercourse, 29% were active cigarette smokers, 49.7% had cervical intraepithelial lesions, and 48.3% had vulvar intraepithelial lesions.

In the HIV group, 36% reported 5 or more lifetime sexual partners and their median age at first sexual intercourse was 17 years. Moreover, 38.7% reported a history of receptive anal intercourse, 32% were active cigarette smokers, 54.7% had cervical intraepithelial lesions, and 35.2% had vulvar intraepithelial lesions.

In the other-causes-of-immunosuppression group, 51% reported 5 or more lifetime sexual partners and their mean age at first sexual intercourse was 18 years. Moreover, 32.6% reported a history of receptive anal intercourse, 29% were active cigarette smokers, 39.1% had cervical intraepithelial lesions, and 29.1% had vulvar intraepithelial lesions. Comparison of risk factors and baseline characteristics is shown in Table 1.

In the HG-AIN group, 34% reported 5 or more lifetime sexual partners. Moreover, 42.9% reported a history of receptive anal intercourse, 46% were active cigarette smokers, 36.4% had cervical intraepithelial lesions, and 21.4% had vulvar intraepithelial lesions.

In the LG-AIN group, 34% reported 5 or more lifetime sexual partners. Moreover, 58.9% reported a history of receptive anal intercourse, 38% were active cigarette smokers, 39.7% had cervical intraepithelial

Table 1. Comparison of Selected Factors by Immunologic Status

	Immunocompetent, *n* = 404 (83.95%)	Immunosuppressed HIV-positive, *n* = 31 (6.45%)	Immunosuppressed by other causes, *n* = 46 (9.6%)	*p*
Age, median (range), y	30 (18–83)	37 (20–69)	40 (21–63)	.03
Smoking, *n* (%)	119 (29.5)	10 (32.3)	11 (23.9)	.68
Sexual anal intercourse, *n* (%)	197 (48.8)	12 (38.7)	15 (32.6)	.03
Condom use for anal sex, *n* (%)	60 (14.9)	7 (22.6)	5 (10.9)	.15
Age at first sexual intercourse, median (range), y	17 (3–40)	17 (14–36)	18 (14-27)	.75
Promiscuity,[a] *n* (%)	94/331 (28.4)	7/19 (36.8)	17/33 (51.5)	.13
Condom use, *n* (%)	189 (46.8)	19 (61.3)	13 (28.3)	.02
CIN 1, 2, 3, *n* (%)	200 (49.7)	17 (54.7)	18 (39.1)	.82
VAIN 1, 2, 3, *n* (%)	78 (19.3)	5 (16.2)	9 (19.5)	.83
Vulvar condyloma-VIN, *n* (%)	195 (48.2)	14 (35.2)	18 (29.1)	<.001
PEIN 1, 2, 3, *n* (%)	54 (13.3)	4 (12.9)	5 (10.8)	.54
AIN 1, 2, 3, *n* (%)	104 (25.7)	16 (51.6)	15 (32.6)	.007

HIV indicates human immunodeficiency virus; CIN, cervical intraepithelial neoplasia; VAIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; PEIN, perineal intraepithelial neoplasia; AIN, anal intraepithelial neoplasia.
[a]It was informed over the patient who answered the question.

lesions, and 26.1% had vulvar intraepithelial lesions. Comparison of risk factors and baseline characteristics is shown in Table 2.

The HIV-positive group had more VIN and HG-AIN compared with the group of immunocompetent and immunosuppressed of other causes ($p = .01$ and $p < .001$). Comparison of the immunologic status and different grades of lower genital tract intraepithelial lesions is shown in Table 3.

The HG-AIN group showed more VIN lesions and HG-PEIN compared with the LG-AIN group ($p < .001$). Comparison of the different grade of lower genital tract intraepithelial lesions and different grade of AIN is shown in Table 4.

Women with HG-CIN (i.e., CIN 2, 3) had 2 times the odds of developing AIN (LG-AIN and HG-AIN) compared to women with LG-CIN (i.e., CIN 1; odds ratio = 1.91, 95% confidence interval = 1.1–3.6; see Table 4).

DISCUSSION

The anal canal shares characteristics with the uterine cervix such as the presence of a transformation zone with metaplastic tissue, epidermal and cylindrical epithelia that join in the squamocolumnar junction, and the role of HPV infection in the genesis of anal cancer and its precursor lesions.

High-resolution anoscopy uses the same basis and procedures cervical colposcopy does [11]. The aims are to visualize the transformation zone; to identify acetowhite changes, mosaicism, punctuation, irregular vessels; and to make a biopsy to confirm the diagnosis.

Table 2. Comparison of Selected Factors by Grade of AIN

Lower genital tract intraepithelial neoplasia, *n* = 481 (100%)	AIN		*p*
	High grade, *n* = 28 (20.9%)	Low grade, *n* = 106 (79.1%)	
Age, median (range), y	33 (19–76)	27 (18–72)	<.001
Promiscuity, *n* (%)	8 (34.8)	30 (34.5)	.581
Smoking, *n* (%)	13 (46.4)	41 (38.3)	.681
Sexual anal intercourse, *n* (%)	12 (42.9)	63 (58.9)	.048
Condom use for anal sex, *n* (%)	3 (10.7)	22 (20.6)	.356
Condom use, *n* (%)	12 (42.9)	58 (54.2)	.065
CIN 1, 2, 3, *n* (%)	13 (36.4)	42 (39.7)	.232
VAIN 1, 2, 3, *n* (%)	6 (21.4)	28 (26.1)	.661
Vulvar condyloma-VIN, *n* (%)	19 (67.8)	78 (74.8)	<.001
PEIN 1, 2, 3, *n* (%)	9 (32.1)	33 (31.8)	<.001

AIN indicates anal intraepithelial neoplasia; CIN, cervical intraepithelial neoplasia; VAIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; PEIN, perineal intraepithelial neoplasia.

Table 3. Different Grades of Intraepithelial Neoplasia by Immunologic Status

Lower genital tract intraepithelial neoplasia, *n* = 481 (100%)	Immunocompetent, *n* = 404 (83.95%)	Immunosuppressed HIV-positive, *n* = 31 (6.45%)	Immunosuppressed by other causes, *n* = 46 (9.6%)	*p*
Cervical				
HSIL (CIN 2, 3)	95 (23.6)	9 (29)	10 (21.7)	.751
LSIL (CIN 1)	105 (26.1)	8 (25.8)	8 (17.4)	
Vaginal				
High-grade VAIN (VAIN 2, 3)	17 (4.2)	2 (6.5)	3 (6.5)	.511
Low-grade VAIN (VAIN 1)	61 (15.1)	3 (9.7)	6 (13)	
Vulvar				
VIN	28 (6.9)	6 (19.4)	5 (10.9)	.011
Condyloma	167 (41.3)	8 (25.8)	13 (28.3)	
Perineal				
High-grade PEIN (PEIN 2, 3)	11 (2.7)	0	3 (6.5)	<.001
Low-grade PEIN (PEIN 1)	42 (10.4)	4 (12.9)	2 (4.3)	
Anal				
High-grade AIN (AIN 2, 3)	16 (4)	8 (25.8)	4 (8.7)	<.001
Low-grade AIN (AIN 1)	88 (21.8)	8 (25.8)	11 (23.9)	

Data are *n* (%).
HSIL indicates high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; LSIL, low-grade squamous intraepithelial lesion; VAIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; PEIN, perineal intraepithelial neoplasia.

Some of the factors that may contribute to the development of this disease are HIV infection and low CD4 count, solid organ transplant, or other causes of immunosuppression such as receiving a high dose of systemic steroids. Anal sexual intercourse, abnormal cervical Pap smear, persistent HPV infection, multiple types of HPV infection, presence of external genital warts, and smoking have also been described as risk factors [12].

Anal intraepithelial neoplasia is part of HPV-multicentric diseases in the lower genital tract. Scholefield et al. [13] described 29 (19%) of 152 women with CIN 3 who had histologic evidence of AIN. Of those (*n*= 37) with more than 1 focus of intraepithelial neoplasia (cervix plus vulva, vagina, or both), 57% (*n* = 21) had anal lesions. However, because anal cancer and its precursor lesions have been mainly been studied in groups of MSM HIV-positive patients, most research has been published based on this population. There are few publications about the prevalence in HIV-negative women. Holly et al. [14] studied 251 HIV-positive women and 68 HIV-negative women. The HIV-positive group had

Table 4. Different Grades of Lower Genital Tract Intraepithelial Lesion by Anal Lesion

	AIN					
	Positive, *n* = 126 (26%)					
Lower genital tract intraepithelial neoplasia, *n* = 481 (100%)	High grade, *n* = 28 (20.9%)	Low grade, *n* = 106 (79.1%)	*p*[a]	Negative, *n* = 355 (74%)	*p*[b]	OR (95% CI)
Cervical						
HSIL (CIN 2, 3)	7 (25)	13 (12.3)	0.121	94 (27.2)	0.039	1.91
LSIL (CIN 1)	6 (21.4)	29 (27.4)		86 (24.9)		(1.1–3.6)
Vaginal						
High-grade VAIN (VAIN 2, 3)	3 (10.7)	4 (3.7)	0.358	15 (4.2)	0.567	1.35
Low-grade VAIN (VAIN 1)	3 (10.7)	24 (22.4)		43 (12.1)		(0.5–3.7)
Vulvar						
VIN	10 (35.7)	8 (6.5)	<0.001	26 (7.3)	0.155	1.69
Condyloma	9 (32.1)	77 (72)		102 (28.7)		(0.8–3.4)
Perineal						
High-grade PEIN (PEIN 2, 3)	6 (21.4)	1 (0.9)	<0.001	7 (2)	0.107	2.69
Low-grade PEIN (PEIN 1)	3 (10.7)	32 (29.9)		13 (3.7)		(0.8–9.1)

Data are *n* (%).
AIN indicates anal intraepithelial neoplasia; OR, odds ratio; 95% CI, 95% confidence interval; HSIL, high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia; LSIL, low-grade squamous intraepithelial lesion; VAIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; PEIN, perineal intraepithelial neoplasia.
[a]Comparison between high grade and low grade.
[b]Comparison between AIN-positive and -negative.

a higher risk for abnormal anal cytologic results than HIV-negative patients did. The HIV-negative women had 2% HG-AIN and 8% of abnormal anal cytologic results. Moscicki et al. [15] studied young women aged 22.5 (2.5) years. Of 410 women, 17 (4%) had abnormal cytologic results. Zbar et al. [16] described 17% cases of HG-AIN in HIV-negative patients. A recent publication by Santoso et al. [17] showed a prevalence of 12.2% of AIN in women with CIN, VIN, and VAIN.

Among the limitations of this study, we can mention that this research cannot predict risk factors associated with the development of AIN, neither can we conclude that identifying HG-AIN would prevent its natural history or would change survival.

One of the strengths of our study is that we have included a large number of patients (n = 481) with 83% of immunocompetent women. Of the 481 women with CIN, VAIN, or VIN, 134 (27.86%) had AIN, 28 (5.82%) had HG-AIN, and 106 (22%) had LG-AIN. Women with HG-CIN (i.e., CIN 2, 3) had a higher risk of developing AIN. This could be a warning sign and may justify anal screening in these patients with multicentric lesions. As regards localization of the lower genital tract, we found statistical difference between the frequency of vulvar lesions and that of anal lesions. Women with vulvar condylomata and VIN may be more likely to develop AIN.

CONCLUSIONS

Immunocompetent women with CIN, VAIN, or VIN may also present HG or LG anal intraepithelial lesions so we should consider AIN as part of the multicentric diseases of the lower genital tract. CIN, VIN, condyloma accuminatta, and VAIN could be warning signs of anal intraepithelial lesions.

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