CLINICAL ARTICLE

High-resolution anoscopy in women with cervical neoplasia

Sandra A. Heráclio [a,*], Juliana Schettini [a], Micheline L. Oliveira [b], Alex Sandro R. Souza [a],
Paulo Roberto E. Souza [c], Melania Maria R. Amorim [a]

[a] Department of Lower Genital Tract Pathology, Women's Healthcare Center, Instituto Materno Infantil Professor Fernando Figueira, Recife, Brazil
[b] Cytopathology Division, Pernambuco Public Health Laboratory, Recife, Brazil
[c] Department of Biology, Federal Rural University of Pernambuco, Recife, Brazil

A B S T R A C T

Objective: To describe high-resolution anoscopy (HRA) findings and compare them with histopathology results.
Methods: In a cross-sectional, observational study performed between December 2008 and December 2009, women receiving care at a center in Recife, Brazil, after a histopathologic diagnosis of cervical intraepithelial neoplasia or cervical cancer were screened for anal neoplasia by HRA. Patients with anal lesions were divided into groups A (metaplasia and/or human papillomavirus infection) and B (anal intraepithelial neoplasia [AIN]). Patients with squamous cell atypia in group A and all patients in group B underwent histopathologic analysis. Agreement between HRA and histopathology findings was estimated for group B. *Results:* HRA was done in 324 women, 204 (63.0%) of whom had anal lesions. Overall, 169 cases (82.8%) were classified as group A and 35 (17.2%) as group B. Histopathologic data were obtained for 28 of the 35 group B cases. Histopathology was suggestive of AIN in 19 (67.9%), resulting in a κ coefficient of 0.45 (95% confidence interval [CI] 0.26–0.65; $P < 0.001$). Relative to histopathology, HRA had sensitivity of 57.6% (95% CI 40.8%–72.7%), specificity of 86.1% (95% CI 75.7%–92.5%), positive likelihood ratio of 4.1 (95% CI 3.1–5.5), negative likelihood ratio of 0.5 (95% CI 0.4–0.5), and accuracy of 76.5% (95% CI 67.2%–83.8%). *Conclusion:* HRA findings can be systematized, reducing the subjectivity of interpretation.

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1. Introduction

Human papillomavirus (HPV) infection is common among sexually active individuals. In the USA, approximately 6.2 million people acquire anogenital HPV infection every year [1], and 43%–64% of adolescents have cervicovaginal HPV infection after 2–3 years of sexual activity [2,3]. There is strong evidence indicating that persistent infection with high-risk HPV genotypes is a prerequisite for the development of cervical cancer, albeit insufficient in itself [4–6], and that it is one of the factors associated with the increase in incidence of squamous cell cancer at other sites of the lower genital tract, particularly the anal canal [7].

HPV-induced invasive tumors of the lower genital tract are generally preceded by a long phase of pre-invasive or precursor disease—a period during which various cell alterations occur that are limited to the epithelial layers without penetrating the basal membrane [8]. In the anus, as in the cervix, these precursor lesions are graded according to certain morphological criteria relative to their biological behavior, with the aim of identifying patients at greatest risk of cancer, thereby permitting clinicians to select the most appropriate method of treatment and monitoring [9]. Anal intraepithelial neoplasia (AIN) is considered a precursor lesion of invasive squamous cell carcinoma of the anus [9], and is classified as low-risk (AIN1) or high-risk (AIN2 and AIN3) [10]. AIN can be asymptomatic, and screening methods include cytology, high-resolution anoscopy (HRA), and directed biopsy [11].

Because of the similarity between the cervical region and the anal canal, HRA has been used to identify epithelial abnormalities in the anal canal among women with cervical abnormalities. HRA consists of direct observation of the perianal region and distal region of the rectum by using a colposcope with standard reagent solutions, as well as applying the principles of colposcopy [12]. Some investigators have suggested that the subjectivity of colposcopy could be reduced using a scoring system to evaluate the characteristics of lesions, enabling them to be classified as low or high grade [13]. The principal characteristics analyzed are lesion margins, color, vascular pattern, and iodine staining, as per the Reid index [14]. The sum of the scores assigned to these characteristics results in a colposcopy index that increases diagnostic accuracy and reduces overestimation [14].

On the basis of a search of the PubMed, SciELO, and Lilacs databases, only one study seems to describe the morphological characteristics of anal intraepithelial lesions observed on HRA [15]. Therefore, the aim of the present study was to describe and characterize HRA findings to systematize and compare them with the results of histopathology, ultimately to achieve a more objective report of HRA findings among

* Corresponding author at: Av. Dr. Malaquias 195/2701, Graças, 50070–550 Recife, Pernambuco, Brazil. Tel.: +55 81 34260284; fax: +55 81 35434047.
E-mail address: sandra_heraclio@hotmail.com (S.A. Heráclio).

women with cervical abnormalities and create a diagnostic classification system.

2. Materials and methods

The present cross-sectional, observational study was conducted among women attending an outpatient clinic for lower-genital-tract pathology at the Instituto de Medicina Integral Professor Fernando Figueira, Recife, Brazil, between December 1, 2008, and December 31, 2009. Women receiving care at this outpatient clinic with a histopathologic diagnosis of cervical intraepithelial neoplasia (CIN) or cervical cancer were included. Women who had a mental health disorder, were in prison, were pregnant, were positive for HIV infection, or had undergone radiotherapy or chemotherapy for the treatment of genital cancer (invasive cancer of the cervix, vagina, or vulva) were excluded from the study. The study protocol was approved by the institute's internal review board (reference #1324). All participants enrolled in the study voluntarily and signed an informed consent form.

Study participants completed a standard questionnaire. Anal cancer screening was then carried out by anal cytology sampling, HRA, and directed biopsy sampling. All women underwent serologic testing for detection of HIV antibodies by enzyme-linked immunosorbent assay.

Anal cytology was performed by S.A.H., using a disposable cytology brush inserted 4.0 cm inside the anal canal. The smear was fixed in 95% alcohol immediately after it was obtained.

To perform HRA, the perianal region was first inspected and a 2% lidocaine spray was then applied. After a digital rectal examination, the colposcope was inserted. The examination was conducted by direct observation through the colposcope, after which 5% acetic acid was applied over the mucosa and Lugol iodine solution was applied for the Schiller's test. Atypical areas were described according to the 2011 terminology of colposcopy of the International Federation for Cervical Pathology and Colposcopy [16], adapted for the anal canal (Table 1).

To describe the HRA findings, a clock-like diagram divided into four quadrants was developed, on which the site of the lesion was recorded. Abnormal transformation zones were identified by their response to acetic acid staining (faint, moderate, or dense), margins (regular or irregular), vascular pattern (fragile, absent, or slightly coarse and coarse vessels), Schiller's test results (iodine-positive, iodine-negative with partial iodine uptake, or iodine-negative), and the extent of the lesion area (affecting one, two, or more quadrants).

Anal lesions were classified into two groups: group A comprised lesions suggestive of metaplasia and/or HPV infection, characterized by the presence of flat, faint acetowhite areas with irregular margins, absent or fragile vessels, and an iodine-negative test or an iodine-negative test with partial uptake; and group B comprised lesions suggestive of AIN, characterized by the presence of raised lesions with moderate-to-dense acetowhite staining, regular margins, slightly coarse or coarse vessels, and an iodine-negative test.

Biopsy samples were obtained from the lesions of group B patients, irrespective of the anal cytology findings, and from those of group A patients with squamous cell atypia on anal cytology. These samples were obtained with the use of 2% topical lidocaine and 3-mm Gaylor-Medina forceps. The samples then underwent histopathologic analysis.

Sample size was calculated via the StatCalc function of Epi Info version 7 (Centers for Disease Control and Prevention, Atlanta, GA, USA) on the basis of a frequency of anal intraepithelial lesions of 13% reported in HIV-negative women with cervical neoplasia [17]. Assuming a 95% confidence level and relative precision of 30%, the sample size was calculated as 324 women. Epi Info version 7 and OpenEpi version 3.0 [18] were used for data analysis. Distribution tables were constructed showing the frequency of the categorical variables. Measures of central tendency and dispersion were calculated for the quantitative variables. When indicated, χ^2 and Fisher exact tests were used at a significance level of 5%.

To verify the agreement between an HRA diagnosis of AIN and histopathology results, the κ coefficient was calculated for group B by assuming values ranging from –1 to 1 [19]. Sensitivity, specificity, positive and negative likelihood ratios, and accuracy were also calculated, together with their respective 95% confidence intervals (CIs), by taking the results of the histopathologic tests as the gold standard for the validation of AIN diagnosis and anal cancer from the abnormal anoscopy findings (group B).

Table 1
Colposcopic terminology.

Description	Cervical pattern[a]	Anal pattern
General	Adequate or inadequate for the cause (e.g. cervix obscured by inflammation, bleeding, scar). Squamocolumnar junction visibility: completely visible, partially visible, or not visible. Transformation zone types 1, 2, 3.	Obscured by intensive inflammation or soft stool. Anal squamocolumnar junction visibility: completely visible, partially visible, or not visible.
Normal colposcopic findings	Original squamous epithelium: mature, atrophic. Columnar epithelium; ectopy/ectropion. Metaplastic squamous epithelium; nabothian cysts; crypt (gland) openings. Deciduosis in pregnancy	Original squamous epithelium: mature. Columnar epithelium. Metaplastic squamous epithelium; crypt closings; crypt (gland) openings.
Abnormal colposcopic findings	Location of the lesion: inside or outside the transformation zone; location by clock position. Size of the lesion: number of cervical quadrants the lesion covers. Size of the lesion as percentage of cervix. Grade 1 (minor): fine mosaic; fine punctation; thin acetowhite epithelium; irregular, geographic border. Grade 2 (major): sharp border; inner border sign; ridge sign; dense acetowhite epithelium; coarse mosaic; coarse punctuation; rapid appearance of acetowhitening; cuffed crypt (gland) openings. Nonspecific: Leukoplakia (keratosis, hyperkeratosis), erosion; Lugol's staining (Schiller's test): stained or nonstained.	Location of the lesion: up or down dentate line; location by clock position. Size of the lesion: number of anal quadrants the lesion covers. Grade 1 (minor): fine mosaic; fine punctation; thin acetowhite epithelium; irregular, geographic border. Grade 2 (major): sharp border; inner border sign; ridge sign; dense acetowhite epithelium; coarse mosaic; coarse punctation; rapid appearance of acetowhitening; cuffed crypt (gland) openings. Nonspecific: leukoplakia (keratosis, hyperkeratosis), erosion. Lugol's staining (Schiller test): stained or unstained.
Suspicious for invasion	Atypical vessels. Additional signs: fragile vessels, irregular surface, exophytic lesion, necrosis, ulceration (necrotic), tumor or gross neoplasm.	Atypical vessels. Additional signs: fragile vessels; irregular surface; exophytic lesion; necrosis; ulceration (necrotic); tumor or gross neoplasm.
Miscellaneous findings	Congenital transformation zone, condyloma, polyp (ectocervical or endocervical), inflammation, stenosis, congenital anomaly, postoperative change (scarred portio, vaginal stump), endometriosis.	Condyloma, polyp (squamous or columnar), inflammation, post-treatment consequence, fistula; hemorrhoids; skin tags.

[a] Adapted from Quaas et al. [16].