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Anal intraepithelial neoplasia screening in patients with human immunodeficiency virus infection

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ABSTRACT

Introduction: the incidence of anal cancer has increased in recent years, making screening and early detection of anal intraepithelial neoplasia (AIN) a necessity in patients at risk.

Methods: a descriptive observational study of homosexual patients (MSM) or women with cervical intraepithelial neoplasia (CIN) III, with human immunodeficiency virus (HIV) infection, included in an AIN detection screening program was carried out between March 2016 and September 2019.

Results: we have performed 695 anal smears, 156 with results of LSIL (low-grade lesion) or HSIL (high-grade lesion) (22.4 %), and 116 high resolution anoscopy (HRA), 75.3 % of patients with altered cytology. We have 403 biopsies, being 84 %

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pathological, 197 biopsies of AIN I (49 %), 96 of AIN II and III (24 %), 44 condylomas (11 %) and the rest (16 %), normal mucosa.

Conclusion: the high prevalence of premalignant lesions and the improvement in the staging of lesions after treatment recommend this protocol.

Keywords: Anal intraepithelial neoplasia. Papilomavirus. Human immunodeficiency infection.

INTRODUCTION

The incidence of anal cancer has increased over the last few years, with a rate of 0.5 to 1.0 per 100,000 population (1). It is more common among people with a human immunodeficiency virus (HIV) infection (PLWH); 77-137 per 100,000 in HIV-infected men who have sex with men (MSM) and 46 per 100,000 in HIV-infected males (2,3). Human papillomavirus (HPV) is the most common sexually transmitted infection among the general population. HPV infection of the anal canal is responsible for the development of anal cancer in almost 90 % of cases (4). HIV-infected men who have sex with men (MSM) are at the highest risk for HPV infection and HPV lesion progression (4). Major risk factors for anal intraepithelial neoplasia (AIN) development include anal HPV infection, receptive anal intercourse, HIV infection and CD4 count below 500 cells (6).

An AIN identification program in higher-risk PLWH, MSM and women with a history of grade II-III cervical lesions, was started in 2013 at Hospital Universitario Son Espases, a tertiary referral hospital in Majorca (Spain) (2). The objective of this study was to describe the role of anoscopy for AIN screening in a tertiary site, since no consensus exists on which is the best screening method for anal cancer in these patients (4).

MATERIALS AND METHODS

This was a descriptive, observational study of the results obtained with the anal cancer screening program from March 1, 2016 until September 2019. The study population included PLWH (MSM and women with a history of CIN II and III). The study was submitted and approved by the institution's Ethics Committee.

Screening was performed by a multidisciplinary team including members of the Internal Medicine Department's Infectious Diseases Unit, General Surgery Department's Coloproctology Unit and Departments of Microbiology and Anatomic Pathology. An initial visit to Internal Medicine included case history, perianal physical examination, sexual behavior survey and, when appropriate, sample collection for a microbiological study of a sexually transmitted infection. Subsequently, patients underwent anal brush cytology and a digital rectal exam. Demographic variables and cytology results were recorded in a proprietary database (eVIHa) after signing an informed consent. All patients were briefed on the natural history of HPV and advised to undergo anal cytology regularly.

Cytology results were reported according to the Bethesda criteria (9). Patients with a pathological result were referred to the coloproctology clinic for a new anamnesis, particularly regarding prior proctological conditions and anorectal surgeries. Patients were informed on the need for high-resolution anoscopy (HRA). Excision was considered together with HRA when condylomata were identified during history-taking or the physical examination.

HRA was performed in an operating room to provide appropriate asepsis, maximally reduce pathology-free biopsy samples and guarantee patient well-being on an outpatient basis. All samples were separately submitted with their anal locations indicated as o'clock positions, with the patient in the lithotomy position. Biopsies were reported as per the Bethesda classification system (9,10) (Table 1).

AIN I lesions were considered as low-grade and follow-up was scheduled with cytology after one year. AIN II and AIN III lesions were considered as high-grade, and treatment was provided with endorectal infrared photocoagulation (Fig. 1). Follow-up was performed at the Surgery clinic, and then the Infectious Diseases clinic with yearly cytology examinations. The Clavien-Dindo classification was used to grade post-surgical complications. Of note, our study systematically used the same examinations for seven years, and patients were thoroughly monitored using medical records and a database.

RESULTS

A total of 695 cytology examinations were performed during the study period, of which 156 (22.4 %) showed pathological findings. Most of these (154, 72.9 %) were LSILs, only two cases (0.95 %) were HSILs and the rest could not be assessed because of an inadequate sample size (Fig. 2). The mean time from cytology results to HRA was ten months (5-15 months) and patients who underwent HRA had a median age of 47 years (interquartile range [IQR] 41-55). HIV was undetectable in 93.2 % of subjects at the time of HRA, and those with a detectable viral load had a median of 4,890 viral copies, a median CD4 cell count of 750 cells/µl (IQR, 572-891) and a median CD4/CD8 ratio of de 0.82.

Overall, 116 HRAs were performed in 75.3 % of patients with abnormal cytology results. At study closure, HRA was still pending for 38 patients. The mean patient age was 47 years (24 to 73 years). A total of 97.4 % were MSM; the rest were HIV-infected women with a history of CIN III lesions. A total of 403 biopsies were processed, of which 84 % were abnormal (Fig. 3); 197 biopsies had AIN I (49 %), 96 AIN II and III (24 %) lesions, 44 had condylomata (11 %) and the rest (16 %) showed a normal mucosa (Figs. 4-6).

Sixty therapeutic HRAs were indicated, i.e., 60 patients required therapy with endorectal infrared coagulation for AIN II or AIN III lesions, or both. The mean number of biopsies per patient was 3.47, with a minimum of two and a maximum of seven (the latter in patients with associated perianal condylomatous disease, since the maximum number of endoanal biopsies was four). Most patients had biopsies with lesions in different stages.

Of the 116 patients who underwent diagnostic HRA, 55.2 % had a second, follow-up cytology performed during the study period. Of these, 60.4 % had a normal cytology and 39.6 % had an abnormal cytology result, thus requiring a repeat HRA. A second HRA was performed in seven patients (6 %) because of new cytologic changes that developed during the study period; 54 % required therapeutic anoscopy and treatment with infrared light. Most repeat anoscopies yielded biopsies with a lower stage, as shown in table 2.

Finally, 57 patients received ablative eradication therapy with endorectal infrared coagulation, representing 49.1 % of patients with an initial pathological cytology. The

remaining patients (51.7 %) did not require this because their biopsies showed a normal mucosa or AIN I lesions. At the time of the review, infrared coagulation was still pending for three patients.

Mild complications were identified within 30 days after surgery. Ten cases (6.4 %) had self-limited rectal tenesmus or rectorrhage (grade I). A single case was detected with Clavien 3 (0.8 %), manifesting as rectorrhage during screening, who required surgical hemostasis.

DISCUSSION

PLWH have a higher prevalence of infection with HPV with longer persistence and faster progression of cyto-histological lesions towards anal cancer. Many questions remain (14,26,27), and no unified population screening method has been established on a national basis, as different communities have different approaches. The best way to screen for anal cancer remains to be established in this population, and different screening strategies have been proposed by different units that manage these individuals (only digital examination plus regular cytologies or digital examination plus cytologies plus HRA when required) (15). The phase-III, multicenter clinical trial, Anchor study (3), will provide answers on which is the best approach to premalignant lesions, whether observation or treatment.

Previous studies have shown that HPV prevalence does not increase with age, and suggest that individuals remain at risk of infection if risky sexual behaviors persist, which implies the absence of anti-HPV immunity after exposure. This may have an impact when determining who should undergo regular cytologies or whether vaccination is needed for at risk individuals (16). The presence of AIN lesions is associated with VPH infection in over 90 % of cases, particularly serotypes 16 and 18, and the incidence of HPV in the anal canal of HIV-infected patients is very high (17,18).

The Ministry of Health Order that implemented cervical cancer screening for women aged 26 to 65 years across the country came into force in 2019 (13). Raising awareness for this condition among women with a history of HPV-related cervical lesions is necessary. As shown in the study by Hessol et al., HIV-infected females have a higher risk for abnormal histology or cytology results (28). Risk factors most commonly

associated with anal HSIL among women with HIV infection include a low CD4 count < 200 cells/µl, engaging in anal intercourse and having cervical dysplasia (19). A limitation of our study was the low number of participating females: only 2.6 % (low adherence). Hence, it is important to raise awareness about this condition, both among HIV-infected females and gynecologists, given the role of the latter in cytological follow-up.

Anal cancer has a higher incidence in females than in males (2.0 *vs* 1.5 per 100,000 people per year, respectively) (7,21). In the United States, the incidence was 1.8 cases per 100,000 people per year from 2009 to 2013, with a mortality rate of 0.2 cases per 100,000 people per year. The annual percentage incidence increase was higher for women (2.7 %) than for men (2.1 %), but the increase in mortality was greater for men (4.0 %) than for women (3.1 %) (17,18). We should bear in mind that the incidence rate estimated for MSM with HIV infection is 131/100,000 inhabitants according to the MACS cohort, and 46/100,000 among non-MSM PLWH (31). An enhanced monitoring of women is important to obtain an earlier diagnosis in this population.

In our series, 84 % of biopsies were pathological and 24 % of these had advanced stages, specifically AIN II-III. These data are similar to those reported in the literature (19). A significant factor to bear in mind in this type of study is the learning curve required to obtain good results, as the number of biopsies with normal mucosa must be reduced and false positive results avoided (21,23). In our study, only 16 % of biopsies had a normal mucosa after a learning curve with approximately 20 patients before data collection (the ideal number of cases in the learning curve has not been yet established in the literature).

We know that the most vulnerable population includes HIV patients, MSM and individuals with AIN III lesions in several or all biopsies. We must consider that recurrence rates vary according to stage, number of sexual partners and genotype (24). Therefore, it is very important that no losses to follow-up occur, and to further study which type of therapeutic HRA should be selected. Ablation therapy with endorectal infrared coagulation was used in our case. In our study, we report second HRAs and their results in order to improve staging.

Treatment of AIN II-III lesions may range from topical measures (5-fluorouracil, 5 % imiquimod, etc.) to more aggressive therapies such as electrocoagulation, radiofrequency, etc. We selected infrared light due to the 70 % effectiveness of eradication, with a recurrence rate of 10-35 %, which is lower than that of other topical and more aggressive therapies. Penetration depth is low and there is no scarring, which should be borne in mind since these patients may require several therapeutic HRA sessions during their lifetime (22,25).

There was a loss to follow-up rate of 44.8 %, which in our view is high and should be reduced. Overall, 60.4 % of new cytologies were negative.

Although the analysis of second HRAs identified an improvement in biopsy results, the small number of patients precluded forming definitive conclusions. Vaccines represent an additional important point. The nine-valent vaccines have demonstrated excellent effectiveness results in men from 16 to 26 years of age against external genital lesions, genital warts and AIN II/III neoplasms (26). This vaccine and both the quadrivalent and bivalent vaccines are approved for use in men. However, they are not included in the immunization schedule (26)

CONCLUSIONS

Although second HRAs are scarce, a reduction in biopsy staging may be noted. Protocol dropouts must be reduced and monitoring of women with dysplasia improved using rectal examination and cytology (27). Screening should be performed on a yearly basis for the high risk population in order to reduce the incidence of anal cancer, although this needs to be firmly established (28). Some studies confirm that cytology plus genotyping plus HRA obtains higher yields compared to cytology alone (30). Hence HRA remains the gold standard for the diagnosis of AIN (31).

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Table 1. The Bethesda classification system

	Low-grade lesions	**High-grade lesions**
Cytology	LSIL	HSIL
Biopsy	Low-grade AIN (AIN I)	High-grade AIN (AIN II and III)

LSIL: low-grade lesion; HSIL: high-grade lesion; AIN: anal intraepithelial neoplasia.

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Table 2. Pathology findings after the first and second HRAs, indicating whether ablation therapy was required

Patient	1st HRA	Need for therapeutic anoscopy (ablation therapy)	2nd HRA	Need for ablation therapy
1	AIN I - AIN III	Yes	AIN I	No
2	3 biopsies AIN III	Yes	1 biopsy AIN III Rest AIN I	Yes
3	2 biopsies AIN II	Yes	AIN I	No
4	AIN I + condylomata	No	AIN I	No
5	AIN I	No	1 biopsy AIN III	Yes
6	AIN I + AIN III	Yes	AIN I	No
7	AIN I	No	1 biopsy AIN III	Yes

HRA: high resolution anoscopy; AIN: anal intraepithelial neoplasia.

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Fig. 1. Working algorithm after positive anal cytology (LSIL: low-grade lesion; HSIL: high-grade lesion; HRA: high resolution anoscopy; AIN: anal intraepithelial neoplasia).

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Fig. 2. Cytological and histological results (LSIL: low-grade lesion; HSIL: high-grade lesion).

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Fig. 3. High-definition anoscopy (HRA) results (AIN: anal intraepithelial neoplasia).

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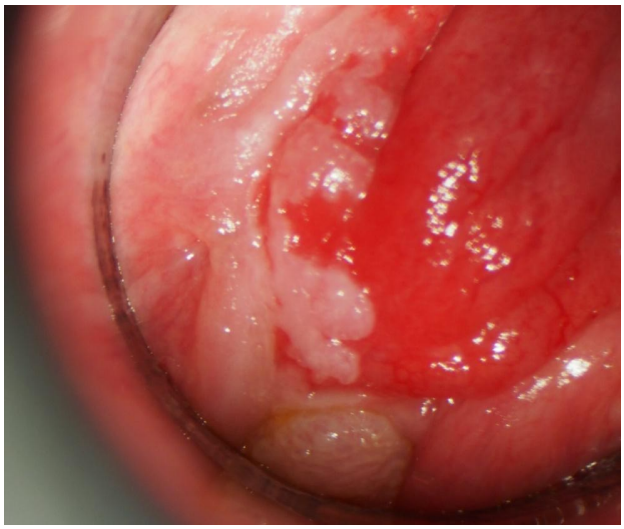

Fig. 4. AIN I lesion.

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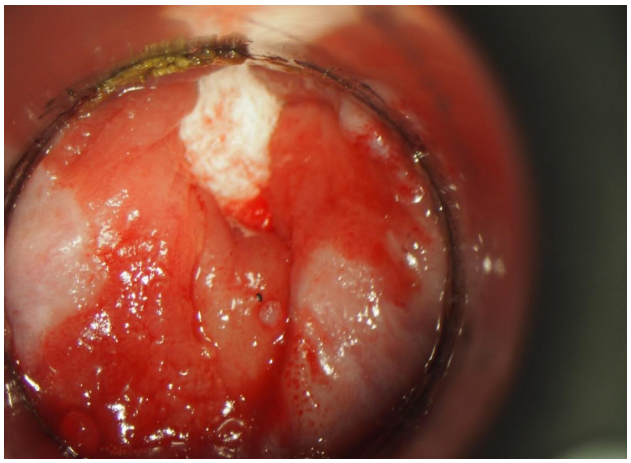

Fig. 5. AIN II-AIN III lesion.

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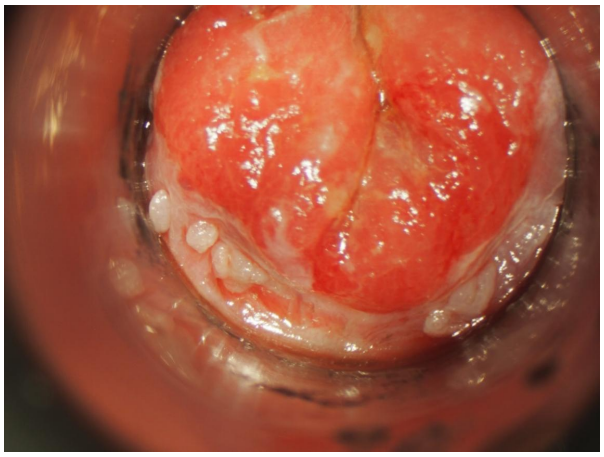

Fig. 6. Condyloma acuminata.