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Prevalence of Anal Dysplasia in HIV-infected Transgender Women

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Abstract

While human immunodeficiency virus (HIV)-infected men who have sex with men (MSM) are at high risk for anal cancer, little is known about the prevalence of anal dysplasia in HIV-infected transgender women (TGW). Our study found that prevalence rates of abnormal anal cytology and histology in HIV-infected TGW were similar to those in HIV-infected MSM.

Keywords

anal cancer; anal dysplasia; transgender women; estrogen hormone replacement therapy; human immunodeficiency virus

Introduction

The incidence of anal cancer in the general population has increased over the last 30 years [1]. Anal cancer now comprises 2.5% of all digestive system malignancies in the United States, and 8080 new cases are diagnosed annually [2]. Although there remains some controversy regarding the utility and cost-effectiveness of anal cancer screening, both the New York State Department of Health's AIDS Institute as well as the HIV Medical Association of IDSA recommend annual screening with anal cytology in populations at particular risk, such as HIV-infected men who have sex with men (MSM) [3] [4]. However, transgender persons are not specifically mentioned in either set of guidelines. Cytological screening aims to detect anal high-grade squamous intraepithelial lesions (HSIL), corresponding to anal intraepithelial neoplasia grade 2 or 3, which are considered premalignant and may progress to anal cancer, analogous to the progression of cervical HSIL to cervical cancer [5]. In addition to persistent infection of anal squamous epithelial cells by high-risk human papillomavirus (hrHPV), a number of other risk factors have been identified in the development of anal HSIL, including HIV infection, receptive anal

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intercourse, low CD4⁺ T-cell count, history of anogenital warts, injection drug use, and current cigarette smoking [6–9]. Although most studies have identified HIV-infected MSM as the population at highest risk for anal cancer compared to women or heterosexual men, we have previously reported substantial prevalence of anal HSIL among HIV-infected patients regardless of sexual behavior based on high-resolution anoscopy (HRA)-guided pathology findings following abnormal anal cytology [10].

Little is known about the prevalence of anal dysplasia in HIV-infected TGW receiving estrogen hormone replacement therapy (HRT). Evidence has suggested that, in addition to the effects of HPV infection, estrogen and/or progesterone may contribute to the persistence and malignant transformation of cervical HSIL to invasive cancer [11–14]. Therefore, the use of estrogen HRT may promote persistence and progression of anal dysplasia in a similar fashion. Against this background, we hypothesized that HIV-infected TGW might have higher rates of anal HSIL than HIV-infected MSM not subjected to estrogen HRT. The purpose of this study was to compare the rates of anal dysplasia between HIV-infected TGW and MSM.

Methods

Study design and study population

This study was performed at various clinical sites of the Icahn School of Medicine at Mount Sinai, where all HIV-infected patients are offered anal cytology screening and, if abnormal, are referred for HRA. During the HRA visit, all patients completed a standardized clinical questionnaire including sexual history. HIV-infected persons who underwent anal cytology screening and subsequent HRA from 2009 to 2016 were reviewed to identify TGW and MSM. TGW were all self-identified and all received estrogen HRT. Cisgender women and transgender men were excluded from the analysis. None of the MSM in this study received estrogen HRT although some did use testosterone HRT. Subjects who underwent HRA-guided biopsy following abnormal anal cytology screening within 6 months prior to HRA were included in the analysis. In some cases anal cytology was resulted as abnormal, but was performed more than 6 months prior to HRA. In these cases, anal cytology was repeated concomitantly with HRA and in some cases yielded benign (1 (5%) TGW and 164 (11%) MSM) or inadequate (0 (0%) TGW and 83 (6%) MSM) results. Demographic information, history of anogenital warts, smoking status, CD4⁺ T-cell count, HIV-1 plasma viral load (pVL), anal cytology results, and subsequent HRA findings for TGW and a comparison group of MSM were abstracted from the electronic medical record. Subjects without HIV infection were excluded.

Anal pap smear (cytology)

A moistened, non-lubricated polyester swab or cytobrush is inserted blindly 5–6 cm into the anal canal to collect cells from the anal verge to above the squamocolumnar junction. The cells are preserved in liquid-based cytology medium for processing. Results are reported in accordance with the Bethesda system for cervical cytology: benign, atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL),

atypical squamous cells, cannot exclude HSIL (ASC-H), or high-grade squamous intraepithelial lesion (HSIL).

High-resolution anoscopy

All procedures were performed by a single provider (M.G.), who is an infectious disease specialist trained in HRA. HRA was performed using previously described techniques [15]. After treatment with 3% acetic acid and Lugol's iodine, the squamocolumnar junction, the distal anal canal and the anal margin were visualized under magnification to look for abnormal vascular patterns and other potential signs of HSIL or cancer, including ulceration, mass effect, and friability. Areas suspicious for HSIL or cancer were biopsied. If no lesion was seen, then no biopsy was taken and the patient was scored as having a "benign" examination. Random biopsies of normal appearing tissue were not performed in this study. Anal biopsy results are reported in accordance with the LAST terminology as benign, as LSIL, corresponding to anal intraepithelial neoplasia (AIN) 1, or as HSIL, corresponding to AIN 2 and 3 [16].

Statistics

Characteristics were compared between HIV-infected TGW and MSM. Data are expressed as either number (percentage) or mean with standard deviation. Continuous variables (age and CD4⁺ T-cell count) were compared between any two groups using the Wilcoxon rank sum test. Dichotomous variables (history of anogenital warts, smoking status, HIV-1 pVL, anal cytology results, and subsequent HRA findings) were compared using the χ^2 test or Fisher's exact test, as appropriate. Significance was assigned to results having P-values <0.05. Statistical analyses were performed using STATA version 13.0 (Stata Corporation, College Station, TX, USA).

Results

Demographic data

In total, 22 (2%) TGW and 1448 (98%) MSM who met inclusion criteria were identified during the study period. As shown in Table 1, there were no statistically significant differences when comparing baseline demographics, history of smoking, history of anogenital warts, mean CD4⁺ T-cell count (cells/ μ l), use of antiretroviral therapy, and rate of HIV-1 viral load suppression (defined as <50 copies/ml).

Anal cytology results

Anal cytology results are summarized in Table 2. Anal cytology was abnormal (ASCUS or greater) in 95% of TGW and 83% of MSM. Anal cytology results in TGW vs. MSM yielded ASCUS in 41% vs. 47%, LSIL in 36% vs. 29%, ASC-H in 5% vs. 4%, and HSIL in 14% vs. 3%, respectively (P = 0.1). The most common cytologic abnormality was ASCUS in both groups. Although anal cytology results in TGW trended toward higher grade compared to MSM, the difference was not statistically significant (P = 0.1).

High-resolution anoscopy results

HRA results are summarized in Table 2. HRA-guided biopsies revealed dysplasia of any degree in 91% of TGW vs. 84% of MSM. Benign histology was found in 9% of TGW vs. 16% of MSM, LSIL in 32% vs. 45%, and HSIL/cancer in 59% vs. 39% ($P = 0.2$). Six cases of invasive anal cancer were found among MSM (0.4%: 6/1448), while no subjects in the TGW group were found to have invasive anal cancer. The most common histopathologic finding among TGW was HSIL, while LSIL was the most common finding among MSM. As was the case with anal cytology, anal histology in TGW trended toward higher grade compared to that in MSM although the difference was not statistically significant ($P = 0.2$).

Discussion

This study suggests that the rates of anal HSIL in HIV-infected TGW are at least as high as in HIV-infected MSM, but there was no significant difference in the rate and distribution of abnormal anal cytology and histology findings between HIV-infected TGW and MSM.

While the impact of treating premalignant anal lesions on the incidence of anal cancer is subject to ongoing study (ANCHOR) [17], there are clinical practice guidelines in place proposing annual anal cytology screening for HIV-infected individuals at particularly high risk for anal cancer [3] [4]. The rationale for screening is based on anatomical and pathophysiological similarities between anal and cervical HPV-associated dysplasia, and the established success of cervical cytology screening in reducing the incidence of cervical cancer. Previous studies suggest that HIV-infected MSM are at higher risk for anal dysplasia and subsequent cancer than other groups [10]. To our knowledge, this study is the first to assess the prevalence of abnormal anal histology among HIV-infected TGW, although one Thai study reported a prevalence of abnormal anal cytology of 42% (36/85) among TGW regardless of HIV serostatus [18]. To date, transgender persons have not been specifically mentioned in anal cancer screening guidelines. This is a particularly important omission since the TGW population carries a very high burden of HIV infection, with an estimated prevalence of 19% [19].

Estrogen and anti-estrogen therapies are associated to the progression and prevention of certain cancers [20]. However, the role of estrogen in cervical and anal cancer, both of which are strongly associated with hrHPV, is poorly understood. In a recent murine study, estrogen appeared to play a critical role not only in the development of cervical HSIL, but also in its persistence and evolution to invasive cancer [21]. Additional data have suggested that an HPV oncogene in conjunction with physiological levels of exogenous estrogen promoted the development of cervical cancer, whereas either factor alone did not [14]. Despite these non-human studies showing a relationship between estrogen and the progression of cervical HSIL to cancer, there is little data assessing the hormonal responsiveness of human cervical cancers [11]. In our study, anal histology in HIV-infected TGW receiving estrogen HRT trended toward higher grade compared to that in MSM although the difference was not statistically significant.

This study has several limitations. The study was neither designed nor powered to demonstrate an impact of estrogen HRT on anal HSIL/cancer. Additionally, there is no data

on how many TGW underwent gender reassignment surgery, which may affect the frequency of anal intercourse.

Given that anal cancer and cervical cancer share many similarities and are both significantly correlated with hrHPV, further studies of the effect of estrogen on anal dysplasia are needed. HIV-infected TGW and MSM had similar prevalence rates of abnormal anal cytology and histology, and therefore we argue that the same screening algorithm should apply for both groups.

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Table 1

Baseline Patient Clinical Characteristics

Characteristic	TGW n = 22	MSM n = 1448	P value
Age, mean (SD)	42 (11)	44 (11)	0.5
History of anal/genital warts, n (%)	8 (36%)	597 (41%)	0.8
History of tobacco smoking, n (%)			0.3
Never	7 (32%)	687 (47%)	
Former	6 (27%)	355 (25%)	
Current	9 (41%)	406 (28%)	
Receptive anal sex, n (%)	22 (100%)	1444 (99%)	0.9
Antiretroviral therapy use, n (%)	21 (96%)	1364 (94%)	0.9
Recent CD4 count (cells/ μ l), mean (SD)	606 (288)	600 (278)	0.9
HIV viral load < 50 copies/mL	17 (77%)	1067 (74%)	0.8

Abbreviations: SD, standard deviation; TGW, HIV-infected transgender women; MSM, HIV-infected men who have sex with men.

Table 2**Anal Cytology and High-Resolution Anoscopy Results**

Cytology result	TGW n = 22	MSM n = 1448	P value
Inadequate sample, n (%)	0 (0%)	83 (6%)	0.1
Benign, n (%)	1 (5%)	164 (11%)	
ASCUS, n (%)	9 (41%)	679 (47%)	
LSIL, n (%)	8 (36%)	412 (29%)	
ASC-H, n (%)	1 (5%)	63 (4%)	
HSIL, n (%)	3 (14%)	47 (3%)	
HRA findings	TGW n = 22	MSM n = 1448	P value
Benign, n (%)	2 (9%)	232 (16%)	0.2
LSIL, n (%)	7 (32%)	656 (45%)	
HSIL or SCC, n (%)	13 (59%)	560 (39%)	

Abbreviations: TGW, HIV-infected transgender women; MSM, HIV-infected men who have sex with men; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells, cannot exclude HSIL; HSIL, high-grade squamous intraepithelial lesion; HRA, high-resolution anoscopy; SCC, squamous cell carcinoma.