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MAJOR ARTICLE

Anal Dysplasia in Human Immunodeficiency Virus-Infected Men Who Have Sex With Men With Sexually Acquired Early Hepatitis C Virus Infection

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Background. Human immunodeficiency virus (HIV)-infected men who have sex with men (MSM) are at increased risk of anorectal infection with high-risk human papillomavirus and subsequent high-grade squamous intraepithelial lesions (HSIL), the putative precursor to anal cancer. Recently, an epidemic of sexually transmitted hepatitis C virus (HCV) has emerged that shares this anorectal route of transmission. We hypothesized that the prevalence of anal HSIL would be high in HIV-infected MSM with sexually acquired early HCV infection.

Methods. High-resolution anoscopy (HRA) findings from a cohort of HIV-infected MSM with sexually acquired early HCV infection were compared with HRA findings from a contemporary cohort of HIV-infected MSM without HCV infection who underwent HRA due to abnormal anal cytology found during routine screening.

Results. Sixty HIV-infected MSM with sexually acquired early HCV infection and the comparator group of 1150 HIV-infected MSM with abnormal anal cytology but without HCV underwent HRA. The HIV-infected MSM with sexually acquired early HCV had higher CD4 counts compared with the comparator group (656 and 541 cells/μL, respectively; $P = .02$). Despite this, the prevalence of anal dysplasia was as high among MSM with early HCV as in the comparator group of MSM with abnormal cytology (47 [78%] and 941 [82%], respectively; $P = .50$), as was the proportion with HSIL (25 [42%] and 379 [33%], respectively; $P = .17$).

Conclusions. The prevalence of anal dysplasia in HIV-infected MSM with sexually acquired early HCV infection was as high as that of HIV-infected MSM with abnormal anal cytology. These findings suggest that primary screening with HRA may be warranted for HIV-infected MSM with early HCV.

Keywords. anal cancer; human papilloma virus (HPV); sexual transmission.

Anal cancer incidence rates are 30 times higher in human immunodeficiency virus (HIV)-infected individuals compared with the general population [1, 2], with the highest reported rates among HIV-infected men who have sex with men (MSM). Developing an effective strategy for screening HIV-infected MSM is therefore essential. The current anal cancer screening algorithms are based on the cervical cancer screening algorithms that have resulted in a significant decrease in cervical cancer mortality [3]. The most common anal cancer screening algorithm is to perform annual anal cytology, and if abnormalities are found, to perform high-resolution anoscopy (HRA) with biopsy of abnormal-appearing areas [4]. We recently evaluated this strategy and found that in an urban cohort of HIV-infected individuals, MSM were significantly more likely to have abnormal anal cytology (63%) compared with women (27%) and heterosexual men (31%) [5]. Furthermore, 31% of MSM who subsequently underwent HRA in response to an abnormal cytology screening test had high-grade squamous intraepithelial lesions (HSIL), the putative precursor to anal cancer [6].

Anal dysplasia and cancer are a direct consequence of sexually transmitted human papilloma virus (HPV) [7]. Human papilloma virus is highly contagious, with anal infection occurring in many MSM as early as the first sexual encounter [8]. Incident infections correlate with the numbers of sex partners, resulting in a life-time prevalence of HPV among MSM approaching 100% [9].

Over the last approximately 15 years, hepatitis C virus (HCV) has also emerged worldwide as a sexually transmitted pathogen among HIV-infected MSM [10]. In our characterization of the epidemic in New York, we found that unprotected receptive anal intercourse was the most important sexual risk factor for HCV acquisition [11], and that HCV is shed into semen [12] and rectal fluid [13], suggesting that transmission occurs during intercourse. With the shared risk factor of unprotected anal intercourse for the acquisition of both HPV and HCV,

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we hypothesized that HIV-infected MSM with sexually transmitted HCV would be at especially high risk for HPV-related anal dysplasia. Therefore, we compared anal biopsy findings of HIV-infected MSM with sexually acquired early HCV infection with those of a cohort HIV-infected but HCV-uninfected MSM who underwent anal biopsy at the same institution during the same time period.

METHODS

Participants and Study Design

This study was a prospective cohort study with comparators matched from an existing retrospective cohort [5], both performed in a single institution. Human immunodeficiency virus-infected MSM with HCV infection were referred to a single practice (D.S.F.) within the Mount Sinai Medical Center through a network of providers of HIV healthcare in the New York City area (New York Acute Hepatitis C Surveillance Network) established to study incident HCV infection among HIV-infected MSM [11, 14, 15]. Written informed consent was obtained with approval of the Institutional Review Board of the Icahn School of Medicine at Mount Sinai ("Mount Sinai School of Medicine" at the time of enrollment of some of the patients) in accordance with the Helsinki Declaration of 1975, as revised in 2000. Eligibility criteria for the early HCV cohort were as follows: (1) early HCV infection, defined as the date of clinical onset of HCV infection having occurred within the prior year, as previously described [10, 16]; and (2) acquisition of HCV through sexual contact as the primary risk factor, as determined by history, including evaluation for sharing of injection drug equipment [11–13]. The date of clinical onset of HCV infection was defined as the date of the first-noted significant alanine aminotransferase *(*ALT) elevation, date of antibody (Ab) seroconversion, or date of first-noted HCV viremia, whichever came first, as previously described [17, 18]. CD4 count, HIV viral load (VL), and antiretroviral therapy (ART) status were collected from the electronic medical record.

High-Resolution Anoscopy

All Participants With Early Hepatitis C Virus Were Referred for High-Resolution Anoscopy. High-resolution anoscopy was performed as previously described [5]. Perianal skin and anal canal, including the squamocolumnar junction, were visually inspected under 15-fold magnification after staining with 3% acetic acid and Lugol's iodine, and biopsies were taken of areas suspicious for abnormal staining or other irregularities suggestive of dysplasia such as ulceration. If no visual abnormalities were found, no biopsies were taken.

The comparator cohort comprised HIV-infected MSM without HCV infection who underwent anal cytology screening between April 2009, upon initiation of universal anal cytology screening among HIV-infected MSM at the Mount Sinai Medical Center, and September 2014 [5]. Annual screening for HCV infection is standard of care in the Mount Sinai health system for all HIV-infected persons. The absence of HCV infection was determined by (1) extraction of diagnostic codes from the electronic medical record for each participant and (2) absence of a diagnostic code for any HCV diagnosis [19, 20]. Participants with abnormal cytology, defined as atypical squamous cells of unknown significance or higher degree of abnormality, all underwent HRA performed by a single anoscopist (M.M.G.). The data from this clinical testing were entered into a clinical database [5]. Human papilloma virus data were not collected into the database until 2012, and then the data were collected for everyone in the cohort. Variables used in comparisons with the early HCV cohort were age, race, ethnicity, cytology findings, HPV infection, and tobacco use, as well as CD4 count, HIV VL, and ART status; all were extracted for both cohorts from the electronic medical record into the clinical database.

Laboratory Analysis

The HCV Ab test we used was the 3rd-generation HCV EIA version 2.0 (Abbott Laboratories); the HCV VL test was COBAS AmpliPrep/COBAS TaqMan HCV Test (Roche Diagnostics), lower limit of quantification 15 IU/mL (1.2 $\log_{10}$ IU/mL); the HCV genotype test was a commercial assay (ARUP Laboratories) in which portions of both the core and NS5B regions of the HCV genome are sequenced. The upper limit of normal for ALT was defined as 35 U/L. Recent syphilis was defined as documented >4-fold increase in rapid plasma reagin titer within 3 months of HCV diagnosis. Human immunodeficiency virus VL suppression was defined as <50 copies/mL. For the comparator cohort, comprising HIV-infected MSM without HCV infection who underwent anal cytology screening, the same HPV test was used for all (Roche Cobas 4800 HPV kit [Roche Diagnostics, Indianapolis, IN], capable of detecting 14 types of high-risk HPV [16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68]).

Statistical Analyses

Descriptive statistics were used to determine risk factors for HSIL on histology. The χ^2 (for categorical variables) and nonparametric testing (for continuous variables) were used to compare demographics, clinical characteristics, and the presence of dysplasia between the early HCV cohort and the HCV-negative comparator cohort. We performed a multivariable logistic model for HSIL outcome, adjusting for age, time from HIV diagnosis to clinical onset of HCV, CD4 count, and HIV VL suppression. IBM SPSS Statistics version 25 was used for data analysis.

RESULTS

Demographics and Clinical Characteristics

Sixty HIV-infected MSM with sexually acquired early HCV were enrolled and underwent HRA between January 2010 and September 2014. Fifty-four (90%) had primary HCV infection and 6 (10%) had HCV reinfection. Consistent with our previous findings in HIV-infected MSM with early HCV in New York City, 55 (92%) were infected with HCV genotype 1 (Table 2). The median time from HCV diagnosis to HRA was 10 weeks. Eleven (24%) had probable recent syphilis infection. Fifty-five (92%) of the 60 HIV-infected MSM with early HCV had engaged in unprotected receptive anal intercourse (URAI) within the prior year (Table 2).

Of the 1710 HIV-infected MSM without HCV who had anal cytology testing at Mount Sinai between April 2009 and September 2014, 1150 (67%) had abnormal cytology findings and underwent HRA examination. This group of 1150 HIV-infected MSM without HCV with abnormal anal cytology findings who underwent HRA comprised the comparator cohort.

The men in the 2 cohorts did not differ significantly in median age, ethnicity, smoking status, ART status, or HIV VL suppression. Men with early HCV were more likely than those without HCV to be white (59% and 28%, respectively; $P < .01$) and have a higher median CD4 count (656 and 541 cells/μL, respectively; $P = .02$) (Table 1).

Table 1. Baseline Demographics of HIV-Infected MSM, With and Without Early HCV Infection

Characteristic	MSM With Early HCV (n = 60) n (%)	MSM Without HCV (n = 1150) n (%)	*P* Value
Race			<.01
White	35 (59)	286 (28)	
Black	8 (14)	264 (25)	
Hispanic	15 (25)	366 (35)	
Other	1 (2)	122 (12)	
Unknown/Missing[a]	1	112	
Median age (years)	44 (IQR, 35–49)	41 (IQR, 32–49)	.13
Smoking Status			.41
Never smoker	33 (55)	513 (47)	
Former smoker	11 (18)	271 (25)	
Current smoker	16 (27)	303 (28)	
Unknown/missing[a]	0	63	
Median $CD4^+$ count (cells/μL)	656 (IQR, 503–796)	541 (IQR, 359–740)	.02
$CD4^+$ count			<.01
>500 cells/μL	46 (77)	658 (57)	
<500 cells/μL	14 (23)	492 (43)	
Unknown/missing[a]	0	0	
ART Use			.90
Yes	56 (93)	1062 (93)	
No	4 (7)	81 (7)	
Unknown/Missing[a]	0	7	
HIV VL			.08
<50 copies/mL	45 (75)	713 (64)	
>50 copies/mL	15 (25)	402 (36)	
Unknown/missing[a]	0	0	
High-risk HPV			.13
Yes	35 (97)	387 (89)	
No	1 (3)	47 (11)	
Unknown/Missing[a]	24	716	
Anal Histology			.20
No lesions biopsied[a]	3 (5)	38 (3)	
Benign	10 (17)	171 (15)	
LSIL	22 (37)	560 (49)	
HSIL	25 (42)	379 (33)	
SCC	0 (0)	2 (0)	

Abbreviations: ART, antiretroviral therapy; ASCUS, atypical squamous cells of undetermined significance; HIV, human immunodeficiency virus; HPV, human papilloma virus; HSIL, high-grade squamous intraepithelial lesion; IQR, interquartile range; LSIL, low-grade squamous intraepithelial lesion; MSM, men who have sex with men; SCC, squamous cell carcinoma; VL, viral load.

[a]Not included in percent or χ^2 calculations.

High-Resolution Anoscopy Findings in Human Immunodeficiency Virus-Infected Men Who Have Sex With Men

Fifty-seven (95%) of HIV-infected MSM with early HCV had visually abnormal areas found on HRA (Table 2). Biopsy of these visually abnormal areas yielded benign pathological findings in 10 (17%) men and dysplasia of any degree in 47 (78%) (low-grade squamous intraepithelial lesions [LSIL] in 22 [37%] and HSIL in 25 [42%]); there were no cancers found (Table 2). These results were comparable to those from HIV-infected MSM without HCV who had abnormal screening cytology leading to HRA, in whom 941 (82%) had anal dysplasia of any degree (LSIL in 560 [49%], HSIL in 379 [33%], SCC in 2 [0%]; $P = .20$). Among those with early HCV, unadjusted analysis showed associations between the presence of HSIL and both younger age and shorter time from HIV diagnosis to clinical onset of HCV ($P = .02$ and $P = .03$, respectively) (Table 2); however, these associations were not significant in multivariable analysis ($P = .37$ and $P = .34$, respectively). Among those who had HPV subtyping performed, 35 (97%) HIV-infected MSM with early HCV had high-risk HPV detected, compared with 387 (89%) HIV-infected MSM without HCV ($P = .13$) (Table 1). Evaluating correlations between HPV- and HIV-related disease, the 25 men with the most advanced HSIL findings were less likely to have HIV VL suppression ($P = .01$) and had lower median CD4 counts ($P = .05$), compared with those without HSIL (Table 2).

DISCUSSION

In this study, we have shown that HIV-infected MSM with sexually acquired HCV have the same degree of anal pathology as HIV-infected MSM without HCV but with already-documented abnormal anal cytology. These findings suggest that HIV-infected MSM with sexually acquired HCV may have a higher risk of anal cancer precursors than the general population of HIV-infected MSM, who themselves have the highest risk of anal dysplasia and cancer among HIV-infected individuals.

Table 2. Risk Factors for High-Grade Squamous Intraepithelial Lesions Among HIV-Infected MSM With Early HCV Infection

Characteristic	All (n = 60[a]) n (%)	No HSIL (n = 35[a]) n (%)	HSIL (n = 25[a]) n (%)	*P* Value
Median age (IQR), years	44 (35–49)	46 (38–50)	41 (29–45)	.02
Median time from HIV diagnosis to clinical onset of HCV (IQR), years	10 (5–14)	10 (7–21)	7 (4–12)	.03
Median CD4$^+$ count (IQR), cells/μL	656 (503–796)	734 (520–860)	553 (469–733)	.05
Antiretroviral therapy use	56 (93%)	34 (97%)	22 (88%)	.16
HIV-1 plasma VL <50 copies/mL	48 (80%)	32 (91%)	16 (64%)	.01
HCV Infection				
HCV genotype (n = 59)[a]				.40
1a	49 (83%)	29 (85%)	20 (80%)	
1b	6 (10%)	2 (6%)	4 (16%)	
2b	2 (3%)	1 (3%)	1 (4%)	
4	2 (3%)	2 (6%)	0 (0%)	
HCV reinfection	6 (10%)	3 (9)%	3 (12%)	.66
Symptoms present at HCV diagnosis	19 (32%)	11 (31%)	8 (32%)	.96
Anal HSV culture$^+$ (n = 57)[a]	3 (5%)	2 (6%)	1 (4%)	.75
Syphilis ever (n = 57)[a]	26 (46%)	17 (53%)	9 (38%)	.29
New syphilis within 3 months of HCV diagnosis (n = 57)[b]	11 (24%)	5 (20%)	6 (30%)	.44
Prior anal condylomata	27 (45%)	17 (53%)	10 (40%)	.51
Prior penile condylomata	3 (5%)	1 (3%)	2 (8%)	.37
High-risk anal HPV (n = 35)[a]	35 (97%)	15 (94%)	20 (100%)	.26
Sexual Practices and Risk Factors				
URAI	55 (92%)	30 (86%)	25 (100%)	.05
Fisting (n = 37)[a]	10 (27%)	6 (26%)	4 (29%)	.87
Toys (n = 37)[a]	9 (24%)	8 (33%)	1 (8%)	.08
Group sex (n = 47)[a]	27 (57%)	15 (58%)	12 (57%)	.97
Methamphetamine use (n = 56)[a]	20 (36%)	12 (39%)	8 (32%)	.60
HRA Visual Findings				
External condylomata	7 (12%)	4 (11%)	3 (12%)	.95
External plaque	4 (7%)	1 (3%)	3 (12%)	.16
Internal condylomata	12 (20%)	6 (17%)	6 (24%)	.51
Internal plaque	49 (82%)	29 (83%)	20 (80%)	.78
Ulceration	3 (5%)	1 (3%)	2 (8%)	.37

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HRA, high-resolution anoscopy; HSIL, high-grade squamous intraepithelial lesion; HSV, herpes simplex virus; IQR, interquartile range; MSM, men who have sex with men; RPR, rapid plasma reagin; URAI, unprotected receptive anal intercourse; VL, viral load.

[a]For variables with unknown or missing data, the actual n is specified and used for calculating percentage.

[b]New syphilis infection defined as documented increase of >4-fold in RPR titer within 3 months of HCV diagnosis.

We do not believe that this association between sexually acquired HCV and HPV-induced anal pathology is due to the early HCV infection per se, but it is instead due to a higher level of exposure to HPV and possibly other cofactors that might be involved in anal dysplasia in those with sexually acquired HCV. Hepatitis C virus is significantly less efficiently transmitted during sex than HIV, as demonstrated by the vast majority of MSM who acquire HCV already being HIV-infected (reviewed in [21]). Furthermore, HPV is significantly more infectious than HIV, with most MSM having acquired at least 1 subtype of HPV before acquiring HIV [22]. Therefore, HIV-infected MSM who eventually acquire HCV during sex are likely to have a higher level of sexual exposure than those who do not. Our finding that 97% of HIV-infected men with early HCV had anal infection with oncogenic HPV subtypes compared with the very high 85% prevalence in the general HIV-infected MSM population further supports this hypothesis [23].

Our study is consistent with prior observations suggesting that the incidence of anal pathology increases as immunologic control wanes, even in those receiving ART [24]. Although almost all of the HCV-infected men were receiving ART and had CD4 counts in the normal range, and none had a CD4 count <200 cells/μL, HSIL was associated with both lack of control of HIV viremia and lower CD4 counts. Our findings are also consistent with the observations that high rates of anal dysplasia [5, 25] and increasing anal cancer rates among HIV-infected MSM continue to be observed even in the ART era [26]. Apparently, in contrast to previously published findings that HSIL incidence increases with age [27], our unadjusted analysis showed an association between HSIL and younger age and shorter time between HIV diagnoses and clinical onset of HCV. Multivariable analysis that adjusted for the lower CD4 count and rate of HIV VL suppression in the HSIL group showed that these younger age parameters were not independently associated with HSIL; however, these findings further emphasize the importance of

HIV virological and immunological control in the pathogenesis of anal dysplasia, even in younger people.

To date, the standard of care for anal cancer screening of HIV-infected MSM is to obtain anal cytology annually and, if cytology is abnormal, to perform HRA [28]. As is true for all screening tests, the sensitivity and specificity of anal cytology for the detection of HSIL are higher when the prevalence of dysplasia is highest, but even in HIV-infected MSM, who have the highest prevalence of dysplasia among HIV-infected individuals, the correlation between anal cytology and histology is poor [29]. For these reasons, some experts have advocated for routine, primary HRA screening without preceding cytology in HIV-infected MSM [29, 30]. However, although primary HRA screening was shown to be cost-effective in the Canadian healthcare setting [31], the same might not hold true in the United States, with its population of approximately 670 000 HIV-infected MSM [32] and higher cost of procedure-based care. In addition, with the lack of widespread availability of HRA services and trained practitioners [29, 33], more accurate surrogate markers for anal pathology are needed. Our findings indicate that sexually acquired early HCV infection among HIV-infected MSM may be such a marker. Our study suggests that those with early HCV infection may have a higher burden of high-risk HPV, resulting in HPV-induced anal pathology similar in both prevalence and severity to HIV-infected MSM who have documented abnormal anal cytology. Further studies should be performed to confirm these findings and to determine whether other high-risk subgroups can be identified for whom primary HRA screening would also be indicated.

There are a number of limitations of this study. There were missing data, in particular in the comparator cohort, due to incomplete retrospective data collection. However, we did not find a difference in demographic variables between those with missing values compared with those without missing values, suggesting there was not systematic bias in the missing data. One important variable, the high-risk HPV molecular assessment, was not performed in a significant minority of the early HCV cohort or in the majority of the comparator cohort, because this test was not routinely performed in the earlier years of the study period. Given the large number of specimens actually examined, however, the actual HPV prevalence is unlikely to be significantly different from what we have reported. Our comparator cohort was not prospectively recruited, and although it differed from the early HCV cohort in racial distribution and median CD4 count, it was derived from similar populations of MSM recruited from similar clinical settings in New York City and was similar in the other measured demographic and HIV-related parameters.

CONCLUSIONS

In summary, HIV-infected MSM with sexually acquired early HCV infection had rates of anal dysplasia at least as high as HIV-infected MSM with abnormal anal cytology. This finding suggests that those with sexually acquired early HCV have a higher level of exposure to HPV than the general population of HIV-infected MSM due to sexual risk behavior and/or cofactors that promote susceptibility to HPV and its oncogenic effects. In either case, improved screening for these interrelated conditions, as well as education for patients and healthcare providers on their necessity, is paramount, and we suggest that early HCV infection in HIV-infected MSM itself may be an indication for primary referral for HRA.

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