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Histologic Correlates of Glandular Abnormalities in Cervical Cytology Among Women With Human Immunodeficiency Virus

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Abstract

Objective—To estimate the frequency and histologic correlates of glandular abnormalities in cervical cytology among women with the human immunodeficiency virus and to compare findings with those of women without HIV.

Methods—In a cohort study of HIV infected and uninfected women followed between 1994 and 2007, Pap tests were obtained every 6 months. Glandular abnormalities, including atypical glandular cells (AGC), adenocarcinoma in situ (AIS), and adenocarcinoma, were identified and correlated with biopsy histology. Multivariate models to summarize data across visits used

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Generalized Estimating Equations. The association of Pap and histology results was assessed using chi-square tests.

Results—Of 48,362 Pap tests from 3,766 women, glandular abnormalities were found in 341 (0.7%) smears from 244 (6%) women, including 93 (1.0%) of 9,564 Pap tests among HIV-seropositive women with CD4 lymphocyte counts less than 250/cmm, 103 (0.8%) of 13,023 Paps among those with counts 250–500/cmm, 68 (0.6%) of 12,470 Paps among women with counts greater than 500/cmm, and 70 (0.6%) of 11,769 Paps among HIV-seronegative women (P for trend = 0.006). Colposcopy was documented for only 148 (61%) of 244 index Pap tests in women with glandular abnormalities. After index abnormal Paps, endocervical curettings were obtained from 106 (43%) women, cervical biopsies from 76 (38%), and endometrial biopsies from 19 (8%). Squamous lesions predominated among histologic findings and histology results did not differ by HIV serostatus (P = 0.16).

Conclusion—Although immunosuppression increased the risk of glandular Pap abnormalities increased in women with HIV, these remained uncommon. Compliance with management guidelines can improved.

Introduction

Women infected with the human immunodeficiency virus (HIV) face a higher risk of squamous cervical lesions than uninfected women (1). They also have higher rates of infection with human papillomavirus, the etiologic agent of cervical cancer (2); of cervical intraepithelial neoplasia (CIN) (3,4), and of cervical cancer (5–7), though cancer risk may be attenuated among women in cancer prevention programs (8).

Cervical cancers also can arise from glandular cells lining the endocervical canal. Premalignant changes in these cells are reflected cytologically as atypical glandular cells (AGC) or adenocarcinoma in situ (AIS). In the general population, AGC is an uncommon cytologic diagnosis, accounting for about 0.3% of Pap tests (9). However, AGC is associated with a high risk of preinvasive and invasive disease; paradoxically, most of these are squamous, including a 9% risk of low grade lesions, an 11% risk of high grade CIN, a 3% risk of histologic AIS, a 1% risk of endometrial hyperplasia, and a 5% risk of cancer (9). Current and past guidelines recommend colposcopy for all women with AGC and AIS, with further investigation dependent on colposcopic findings and the severity of the cytologic abnormality (10,11).

Cervical adenocarcinoma and adenocarcinoma in situ have been linked to infection with the human papillomavirus (HPV) and like squamous disease should be more common among immunosuppressed women (12). Unfortunately, rates of cytologic AGC and AIS and the associated risk for glandular neoplasia have not been well studied among women with HIV. In part, this is because glandular lesions are less common than squamous lesions, and accruing sufficient numbers of HIV-seropositive women in screening programs across time has been challenging. Lehtovirta and colleagues found that atypical glandular cells (AGC) were found in 4% of HIV-seropositive women undergoing cytologic screening, but they studied only 108 women and did not describe histologic findings (13).

Our objectives were to estimate the frequency of cytologic atypical glandular cells, AIS, and adenocarcinoma among women with HIV; to present histologic correlates of these cytologic abnormalities among women who subsequently had colposcopy, to assess compliance with current management recommendations, and to estimate whether HIV-seropositive women were at higher risk for cytologic and histologic glandular abnormalities than seronegative women.

Methods

This investigation was part of the Women's Interagency HIV Study (WIHS), an ongoing multicenter cohort study of the natural history of HIV infection and related health conditions among HIV seropositive women and at-risk HIV-uninfected comparison women. The protocols, recruitment processes, procedures, and baseline results of the WIHS have been previously described; seropositive WIHS participants are representative of U.S. women with HIV (14). WIHS enrollment began October 1, 1994 at six study consortia and over time enrolled 3,766 women, with expansion during 2001–2002 (15). Written informed consent for study was obtained after local human subjects committee approval from six sites. Follow up continues, but this analysis includes information obtained before October 1, 2007.

Every six months, participants had structured medical, social, and sexual histories taken by trained interviewers, followed by a physical examination that included gynecologic evaluation and Pap testing. According to study-wide protocol, single-slide Pap samples were obtained using a spatula and brush. HIV status was established by Western blot, and women who seroconverted during follow-up were classified according to visit-specific serostatus. Pap tests were interpreted centrally at Dianon (New York, NY, formerly Kyto or Kyto Meridien) according to the 1991 Bethesda system for classification of cervicovaginal cytology (16), updated in 2001. Glandular abnormalities were classified as atypical glandular cells, subclassified as not otherwise specified or favor neoplastic, as adenocarcinoma in situ, and as adenocarcinoma. All Pap smears were screened by two cytotechnologists blinded to HIV status, with 10% of all negative smears and all abnormal smears reviewed by a cytopathologist. Study protocol recommended referral for colposcopy for glandular abnormalities of any grade, though decisions on biopsy and treatment were individualized. At some sites, women were referred externally for colposcopy, especially early in the study, and women may have had Pap tests outside study centers that led to colposcopy. Although women were asked whether they had cervical biopsies externally in the six months prior to each visit, with affirmative answers leading to medical records retrieval, but we could not confirm negative responses. Histology results were interpreted locally and were not centrally reviewed.

Of the 3766 women in WIHS (2791 HIV+, 975 HIV−), 3522 women (2593 HIV+, 929 HIV −) were excluded because they did not have an index smear showing glandular abnormalities during the study period. One HIV seropositive woman was excluded because she had undergone hysterectomy before her index AGC pap. Another 95 women (78 HIV+, 17 HIV−) were excluded because they did not have colposcopy done within 6 month of index abnormal Pap. Finally, 29 women (25 HIV+, 4 HIV−) were excluded because they had no histologic results, leaving 119 women (94 HIV+, 25 HIV−) for analysis.

Histology and cytology results were tabulated. Differences in demographic and clinical characteristics between HIV seropositive and seronegative women were compared using Fisher's exact test. Multivariate logistic regression models that incorporated Generalized Estimating Equation (GEE) models were used to compare the proportions of patient-visits in HIV seropositive and HIV seronegative group with glandular abnormality, adjusting for repeated measures across visits for the same women over time (17). The variables adjusted for were age (divided into 4 groups: <30, 30–40, 40–50, >50), ethnicity, smoking status, and whether the patient had been sexually active in the last six months. To further investigate the association of HIV serostatus and glandular abnormality, the model was refitted with an HIV serostatus variable, categorized as HIV seronegative, HIV seropositive/CD4 lymphocyte count <250/cmm, HIV seropositive/CD4 250–500, HIV seropositive/CD4 >500. A test for trend was applied: we parameterized HIV-serostatus and CD4+ lymphocyte count as a continuous variable with four levels for HIV seronegative women and HIV seropositive

women with CD4 counts >500, 250–500, and <500/cmm and determined the significance of this variable in GEE models. The Wald test was used to determine the significance of all variables in these models (18).

For comparing the association of cytologic status with histologic findings between HIV seropositive and HIV seronegative groups, the Pearson's chi-square test of independence was applied. Only index glandular abnormalities were included in estimating the correlation of histologic and Pap test results. Median age was compared between groups of subjects using the Wilcoxon test.

Results

During the study period we found 341 (0.7%) Pap results showing a glandular abnormality among 48,362 collected during 24, 948 person-years of observation. These occurred in 244 (6%, **95% CI, 5.7%–7.3**) of 3,766 women. Of the 341 glandular Pap abnormalities studied, 271 were from 198 HIV seropositive women and 70 were from 46 seronegative women. One woman had a hysterectomy prior to her index glandular abnormality and was excluded from further analysis.

Glandular abnormalities were found in 341 (0.7%, **95% CI, 0.6%–0.8%**) smears from 244 (6%) women, including 264 **(0.8%, 95% CI, 0.6%–0.9%)** of 35057 smears from HIV seropositive women and 70 (**0.6% (95% CI, 0.4%–0.8%)** of 11,769 smears from seronegative women (P = 0.12 after adjustment for age, ethnicity, smoking, and sexual activity in the prior six months). The demographic characteristics of women with glandular abnormalities on Pap are presented in Table 1. The median age was 37 years among 198 HIV seropositive women and 39 years among 46 HIV seronegative women (P = 0.9). Compared to HIV seronegative women, seropositive women with glandular abnormalities were marginally less likely to be smokers and less likely to have multiple recent sexual partners.

Stratification by CD4 lymphocyte count showed the impact of immunosuppression on risk for glandular cytologic abnormality: glandular abnormalities were found in 93 **(1.0%; 95% CI, 0.8%–1.3)** of 9564 Pap tests among HIV-seropositive women with CD4 lymphocyte counts <250/cmm, 103 **(0.8%; 95% CI, 0.6% –1.0%)** of 13023 Paps among those with counts 250–500/cmm, 68 **(0.6%; 95% CI, 0.4%–0.8%)** of 12470 Paps among women with counts >500/cmm, and 70 **(0.6%; 95% CI, 0.4%–0.8** of 11769 Paps among HIV-seronegative women (P for trend = 0.006). Seven women with glandular abnormalities did not have CD4 counts at the corresponding visit.

Despite a study-wide protocol recommending referral for colposcopy and despite intensive infrastructure at each site to promote compliance, colposcopy was documented to have been done within six months for only 148 (61%) of 244 index Pap tests with glandular abnormalities, 119 (60%) of 198 HIV seropositive and 29 (63%) of 46 HIV seronegative women. Endocervical curettings were obtained after 106 (43%) women with index abnormal Paps, including 81 (41%) HIV seropositive women and 25 (54%) seronegative women. Cervical punch biopsies were done for 76 (38%) index Paps, 60 (30%) in HIV seropositive women and 16 (35%) in seronegative women. Endometrial biopsies were done in only 19 (8%) index Pap cases, 13 in HIV seropositive and 6 in seronegative women. Excisional biopsies, including knife conization and loop excision, were done in 14 women. Overall, histologic findings were available for 119 (49%) of the 244 women within six months of an index Pap showing glandular abnormalities. Compliance improved as women were followed, as 212 (87%) of women with index glandular abnormalities had colposcopy and 192 (79%) had at least one biopsy at some subsequent point during the study.

Histology results from these 94 HIV seropositive women and 25 seronegative women with available histologic results after index glandular Pap abnormalities are shown in Tables 2 and 3. Overall, the severity of results did not differ significantly by HIV serostatus (P = 0.16). For both HIV infected and uninfected women, most abnormalities were squamous. Approximately 40% of biopsies in both groups were negative, and the risk of CIN or cancer was greater than 50%. However, high grade disease, including high grade squamous lesions, glandular atypia, or cancer, was found in 20/94 (21%) of HIV seropositive women and 9/25 (36%) of HIV seronegative women (P = 0.12). Although glandular abnormalities on Pap raise concern for adenocarcinoma, only one HIV seropositive woman and none of the HIV seronegative women had adenocarcinoma, while none of the HIV seropositive women and one of the seronegative women had glandular atypia.

Discussion

Our results show that the risk of cervical glandular cytologic abnormalities, like that of squamous Pap abnormalities (1) and HPV in general (19), is increased by immunosuppression among women with HIV. These findings are qualitatively similar to those of Lehtovirta and colleagues, who reported a 4% risk of abnormal glandular cytology in their patients with HIV (13), although the absolute frequency of abnormality was lower in our cohort, at 0.8% of all HIV seropositive women.

In our study, the rate of biopsy-proven cervical cancer precursors among HIV seropositive women with glandular cytologic abnormalities was substantial. Among those with HIV, more than half had CIN or cancer, although only 21% had high grade disease. These results are consistent with rates reported in HIV seronegative women (9), and we did not find a difference in risk for high grade disease between HIV seropositive and seronegative women once glandular abnormalities were reported on Pap. While the 3% risk of cancer that we found among HIV seropositive women is small in absolute terms, it does reflect a substantial. Although WIHS is the largest U.S. cohort study of women with HIV, we had too few events to stratify histologic results by CD4 count; studies from other national cohorts may help to determine whether the most severely immunosuppressed women have an increased risk of biopsy-proven cervical disease after glandular Pap abnormalities.

For now, our results suggest that women with HIV and glandular abnormalities on Pap testing should be managed according to guidelines for the general population from the American Society for Colposcopy and Cervical Pathology (ASCCP)(10). These recommend colposcopy with endocervical curettage for all women, with endometrial assessment for those over age 35 years or with risk factors for endometrial cancer such as obesity or irregular vaginal bleeding. Risks for cervical disease and cancer are too high to justify either triage using HPV DNA testing without colposcopy or surveillance with serial cytology, as can be done for women with atypical squamous cells of uncertain significance (ASC-US). One exception to the management of glandular abnormalities according to ASCCP guidelines involves testing for high risk HPV types at initial colposcopy to minimize follow-up for women with negative initial evaluation. This strategy has not been tested in women with HIV, whose high prevalence of high risk HPV may limit the specificity of this approach.

Women with HIV are at risk to default from colposcopy appointments (20). The discrepancy between the number of glandular Pap abnormalities and the number of colposcopies indicates that substantial opportunities for improved compliance with follow-up guidelines can be achieved for women with glandular Pap abnormalities. Unfortunately, our low rates of colposcopy and endocervical and endometrial sampling parallel those in the general cytology literature on glandular abnormalities, although many of our patients were evaluated

before national guidelines were promulgated in 2001. Our data are too limited to allow us to distinguish between missed colposcopy because of patient noncompliance or clinician failure to recall women with glandular abnormalities on Pap for colposcopy. According to protocols developed soon after study launch, colposcopy referral was recommended after any study Pap showing a glandular abnormality. It is possible that women failed to report some colposcopies and biopsies that occurred outside study sites, but the low rate of endocervical curettage and endometrial biopsy in our study suggests that providers' lack of familiarity with Pap management guidelines and patients' reluctance to undergo these somewhat invasive and painful procedures contribute. Clinicians who care for women with HIV should be familiar with Pap management guidelines and should educate patients about the potential cancer prevention benefits of compliance.

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Table 1

Demographic and medical characteristics at the time of first diagnosis among 244 women with glandular abnormalities on Pap tests.

	HIV+ (n=198)	HIV− (n=46)	*P*-value[1]
Ethnicity			0.63
Non-Hispanic white	31 (16)	5 (11)	
Hispanic white	10 (5)	2 (4)	
Non-Hispanic black	121 (61)	27 (59)	
Hispanic black	2 (1)	1 (2)	
Other	34 (17)	11 (24)	
Smoking			0.06
Current	119 (60)	27 (59)	
Former	30 (15)	13 (28)	
Never	48 (24)	6 (13)	
Number of sexual partners in prior 6 months			0.003
0	68 (35)	8 (17)	
1	102 (52)	24 (52)	
2–5	21 (11)	14 (30)	
>5	6 (3)	0 (0)	
CD4 count (cells/ml)			
<250	70 (36)	NA	
250–500	81 (42)	NA	
>500	41 (21)	NA	
HIV RNA level (copies/ml)			
Undetectable	46 (24)	NA	
80–10,000	57 (30)	NA	
10,000–100,000	54 (28)	NA	
>100,000	33 (17)	NA	

[1] By Fisher exact test

Table 2

Histologic findings among women with index glandular abnormalities on Pap tests from HIV seropositive women.

	Histologic result								Total
Pap result	**Negative/Benign**	**CIN[1]1/koilocytosis**	**CIN 2,3**	**Ungraded CIN**	**Squamous cancer**	**Glandular atypia**	**Adenocarcinoma**	**Other**	
AGCUS[2] (endocervical)	25 (27)	23 (24)	13 (14)	2 (2)	2 (2)	0	0	1 (1)	66 (70)
AGC[3] (unqualified)	14 (15)	7 (7)	4 (4)	1 (1)	0	0	0	1 (1)	27 (29)
AIS[4]	0	0	0	0	0	0	1 (1)	0	1 (1)
Total	39 (41)	30 (32)	17 (18)	3 (3)	2 (2)	0	1	2 (2)	94 (100)

P = 0.16 for the distribution of findings among HIV seropositive vs seronegative women. N (%)

Table 3

Histologic findings among women with index glandular abnormalities on Pap tests from HIV seronegative women.

	Histologic result[5]					
Pap result[5]	**Negative/Benign**	**CIN/koilocytosis**	**CIN2,3**	**Glandular atypia**	**Other**	**Total**
AGCUS (endocervical)	9 (36)	4 (16)	8 (32)	1 (4)	0	22 (88)
AGC (unqualified)	1 (4)	1 (4)	0	0	0	2 (8)
AGC (favor neoplastic)	0	0	0	0	1 (4)	1 (4)
Total	10 (40)	5 (20)	8 (32)	1 (4)	1 (4)	25 (100)

P = 0.16 for the distribution of findings among HIV seropositive vs seronegative women. N (%)

[1] Cervical intraepithelial neoplasia

[2] Atypical glandular cells of uncertain significance

[3] Atypical glandular cells

[4] Adenocarcinoma in situ

There were no cases of AIS on Pap, of ungraded CIN, or of [5] squamous or adenocarcinoma among HIV seronegative women

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