RESEARCH COMMUNICATION

Underlying Histopathology of HIV-infected Women with Squamous Cell Abnormalities on Cervical Cytology

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Abstract

This study was undertaken to evaluate the underlying histopathology of HIV-infected women who had abnormal cervical cytology. HIV-infected women with abnormal cervical cytology undergoing colposcopy at Chiang Mai University Hospital between January 2001 and February 2008 were reviewed. The cohorts were matched and compared with an HIV-negative group. During the study period, 65 HIV-infected women with abnormal cervical cytology were available for review. The abnormal cervical smears were atypical squamous cell (9), low-grade squamous intraepithelial lesion (22), high-grade squamous intraepithelial lesion (27), and squamous cell carcinoma (7). When stratified by severity of abnormal cytology, HIV-infected women had a higher risk of having cervical intraepithelial neoplasia II or higher, whether the cervical smear showed low-grade (P=0.01) or high-grade abnormality (P=0.04) compared with the HIV negative group. After adjustment by age, parity, and menopausal status, HIV-infected women had 2.56 times the risk of having CIN II or higher (69.2% of HIV-infected women compared with 47.7% of HIV negative women; 95% CI=1.21-5.40, P=0.01). In conclusion, HIV-infected women with abnormal Pap smears are a population subset with higher risk of significant cervical lesions, irrespective of severity of abnormal cervical smears.

Key Words: Cervical cytology - human immunodeficiency virus - histopathology - risk factors

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Introduction

Current evidence has demonstrated that women with human immunodeficiency virus (HIV) infection have an increased risk of co-infection with human papillomavirus (HPV), persistent HPV infection with multiple strains of HPV, and cervical dysplasia (Palefsky et al., 1999; Ellerbrock et al., 2000; Chalermchockcharoenkit et al., 2006). Several reports have documented a five to ninefold relative increase in risk of developing invasive cancer in these women, particularly in settings of poor screening (Klevens et al., 1996; Frisch et al., 2000; Gallagher et al., 2001).

Cervical cytology is widely accepted as the most effective cancer screening methods in medical history. The introduction of this screening test in the United States has led to a 70 to 80% decrease in the incidence and the mortality of invasive cervical cancer (Austin 1997). Generally, management of women with an abnormal cervical cytology depends primarily on the severity of cytological abnormality, which reflects the risk of underlying high-grade and invasive lesions. However, the data about underlying histopathology in HIV-infected women with abnormal cervical cytology are limited. Accordingly, this study was undertaken to evaluate the prevalence of high-grade and invasive lesions in HIV-infected women with abnormal cervical cytology and compare it with that of HIV-negative women.

Materials and Methods

After gaining approval of the Research Ethics Committee, we reviewed the medical records of women with abnormal cervical cytology undergoing colposcopy at Chiang Mai University between January 2001 and February 2008. It was our policy to check the HIV status in every woman prior to colposcopic examination because of the high incidence of HIV infection in Chiang Mai province. In addition, colposcopy was carried out in every woman with abnormal cytology due to patient anxiety and high rate of loss to follow-up.

Abstracted data included patient characteristics, type of abnormal cervical smears, CD4 cell count within 6 months of colposcopy, colposcopic findings, and histopathology on colposcopically-directed biopsy or subsequent cervical conization and hysterectomy. The HIV-negative women were recruited for controlled subjects matching 1:1 for the following variables (±

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tolerance): type of abnormal cervical cytology (no tolerance), age (±10 years), and examination time period (±12 months). All cervical smears in this study were conventional preparations.

Descriptive statistics were used for demographic data. The chi-square and Fisher's exact test were calculated whenever appropriate to compare between the groups. A multivariate analysis using logistic regression model was used to find the independent predictor. An odds ratio, with 95% confidence interval (CI) that did not include unity, was considered statistically significant. All statistical tests were two sided and a P-value of less than 0.05 was considered statistically significant.

Results

During the study period, 80 HIV-infected women with abnormal Pap smears were identified. Fifteen women were excluded because of unavailable medical records, leaving a study population of 65 HIV-infected women for analysis. Mean age ± SD was 37.1 ± 8.2 years (median 36, range 22-60). Seventeen (26.2%) women were nulliparous. Two (4.6%) women were postmenopausal. Previous opportunistic infections including Pneumocystic jiroveci pneumonitis, cytomegaloviral retinitis, cryptococcal meningitis, and tuberculous pneumonitis were noted in 15 (23.1%) women. Thirty-three (50.8%) women received antiretroviral therapy at the time of colposcopy. Among 34 women who had CD4 cell count within 6 months of colposcopy, the mean CD4 cell count ± SD was 273.7± 191.7 (median, 250, range 4-800 per mL). Eleven women had a CD4 cell count less than 200 per mL.

The correlation between cervical cytology and final diagnosis in both HIV positive and negative women are summarized in Table 1. The prevalence of high-grade diseases including cervical intraepithelial neoplasia (CIN) II-III and invasive cancer in HIV-infected women was 69.2%, which was significantly different from that in HIV negative women (47.7%, P=0.01). Details of the actual lesions are given in Table 2. The FIGO stages of cervical cancer among 7 HIV-infected women were as follows: squamous cell carcinoma stage IA1 (4), squamous cell carcinoma stage IB1 (2), and adenocarcinoma stage IB1 (1). When stratified by severity of abnormal cytology, HIV-infected women had a higher risk of having underlying CIN II or higher, whether the cervical smear showed low-grade (P=0.01) or high-grade abnormality (P=0.04) compared to the HIV negative group. Adjusting by age, parity, and menopausal status, HIV-infected women had 2.56 times the risk of having CIN II or higher (69.2% of HIV-infected women compared with 47.7% of HIV negative women; 95% CI=1.21-5.40, P=0.01).

Table 1. Correlation between Cervical Cytology and Final Diagnosis According to HIV Status

Cytology		HIV (+)	HIV (-)
ASC†(N=9)‡	No CIN	3 (33.3)	6 (66.6)
	CIN I	3 (33.3)	3 (33.3)
	CIN II-III	2 (22.2)	0 (0.0)
	Cancer	1 (11.1)	0 (0.0)
LSIL (N=22)‡	No CIN	4 (18.2)	13 (59.1)
	CIN I	9 (40.9)	6 (27.3)
	CIN II-III	9 (40.9)	3 (13.6)
HSIL(N=27)‡	No CIN	1 (3.7)	4 (14.8)
	CIN II-III	21 (77.8)	15 (55.6)
	Cancer	5 (18.5)	8 (29.6)
SCCA(N=7)‡	No CIN	0 (0.0)	2 (28.6)
	CIN II-III	6 (85.7)	3 (42.8)
	Cancer	1 (14.3)	2 (28.6)

ASC, atypical squamous cell; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCCA, squamous cell carcinoma; CIN, cervical intraepithelial neoplasia; †including ASC-US (7) and ASC-H (2);‡Numbers of women in combined HIV positive and negative groups

Table 2. Prevalence of Underlying High-grade Disease of HIV-infected Women Stratified by Severity of Pap Smears

Smear abnormality	Final diagnosis	HIV (+)	HIV (-)	p value
All smears (N=65)†	High*	45 (69.2)	31 (47.7)	0.01
	Low**	20 (30.8)	34 (52.3)	
Low-grade‡ (N=31)†	High	12 (38.7)	3 (9.7)	0.01
	Low	19 (61.3)	28 (90.3)	
High-grade#(N=34)†	High	33 (97.1)	28 (82.4)	0.04
	Low	1 (2.9)	6 (17.6)	

*High-grade diseases: CIN II-III or higher; **Low-grade disease: CIN I or less; † Numbers of women in each HIV positive and negative groups: * grade of disease; ‡ including atypical squamous cell (9) and low-grade squamous intraepithelial lesion (22);#including high-grade squamous intraepithelial lesion (27) and squamous cell carcinoma (7)

Discussion

Although there are various methods for screening precancerous cervical lesions, the Pap smear test is still the most common, particularly in developing countries. The effectiveness of Pap smear test in detecting CIN in HIV-infected women has been reported to have a sensitivity varying from 60% to 80%, whereas the specificity ranges from 65% to 85% (Stier 2003). Massad et al (2001) reported a higher positive predictive value of cervical smears in HIV-infected women (72%) than that in HIV-uninfected women (60%). In this study, when adjusted by age, parity, and menopausal status, HIV-infected women with abnormal Pap smears of any grade had approximately 2.6 times the risk of having CIN II or higher (95% CI=1.21-5.40, P=0.01) compared to HIV-negative women. Because of the higher risk of harboring such significant lesions, once abnormal cervical cytology is diagnosed, these HIV-infected women warrant further appropriate evaluation and immediate colposcopy would be the management strategy of first choice.

Data regarding the underlying histopathology of HIV-infected women with borderline or low-grade cytological abnormalities including atypical squamous cell (ASC) and low-grade squamous intraepithelial lesion (LSIL) are limited. Thus, conclusions about the impact of HIV infection on the prevalence of underlying high-grade diseases among such women remain far from definitive. In this study, the prevalence of underlying CIN II-III and invasive cancer in HIV-infected women who had Pap smears suggesting ASC or LSIL was significantly higher than that noted in the HIV-negative group (38.7% and

9.7%, respectively, P=0.01). Various strategies, including close follow-up with interval cytology, HPV testing, and immediate colposcopy, have been proposed as the management options for women with ASC or LSIL smears, However, based on the considerably high risk of HIV-infected women having underlying high-grade diseases, the authors strongly recommend immediate colposcopy for these smear abnormalities in order to detect and treat such significant lesions early.

Cytological diagnoses of high-grade squamous intraepithelial lesion (HSIL) and squamous cell carcinoma identify women at a significant risk of underlying CIN II-III and invasive cervical cancer. Previous studies from Chiang Mai University Hospital reported the prevalences of CIN II-III and invasive cervical cancer in women with HSIL smears to be 74% and 17%, respectively (Kietpeerakool et al., 2007). For women with Pap smears featuring squamous cell carcinoma, 64.6% and 33.3% had CIN II-III and invasive cervical cancer, respectively (Charoenkwan et al., 2006). In this study, the prevalence of underlying CIN II or higher in HIV-infected women with these two smear abnormalities was significantly higher than that in the HIV negative group (97.1% and 82.4%, respectively, P=0.04). These findings reaffirm the necessity for aggressive evaluation in HIV-infected women with HSIL or squamous cell carcinoma smears to make certain that all high-grade and invasive lesions are detected and treated at as early a stage as possible.

Regarding the effect of antiretroviral therapy on the natural course of CIN, the overall results from previous studies remained inconclusive (Lillo et al., 2001; Moore et al., 2002; Heard et al., 2002). However, regarding the effect of immune function, previous studies have consistently demonstrated that the amount of CD4 cell count is a significant predictor for having or developing CIN (Heard et al., 2000; Davis et al., 2001; Chalermchockcharoenkit et al., 2006). Due to a relatively small sample size here, the authors could not determine the effect of either antiretroviral therapy or level of CD4 cell count on the underlying histopathology of HIV-infected women.

Interestingly, the prevalence of underlying invasive cervical cancer observed across all grades of cervical smear abnormalities was significantly high whether or not it was evaluated in HIV-positive or negative groups when compared to that of the previous reports (Dunn et al., 2003; Schiffman and Solomon, 2003; Sadan et al., 2007). These unique findings may reflect the influence that individual background incidence of cervical cancer has on the underlying histopathology of women with abnormal cervical smears.

This study was hampered by a number of limitations; a small sample size, a retrospective study design which limited data collection. However, despite these limitations, the significantly higher risk of harboring high-grade disease among HIV-infected women was demonstrated. Based on this finding, immediate colposcopy is recommended in HIV-infected women with abnormal cervical cytology, irrespective of degree of cytologic abnormality to allow timely detection and treatment of underlying high-grade disease.

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