Relationship between Human Papilloma Virus Infection and Abnormal Pap Smear in HIV-Seropositive Women at Siriraj Hospital

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Abstract

The purpose of this prospective study was to determine the prevalence of human papillomavirus and abnormal Pap smear in HIV-seropositive women, particularly in HIV-seropositive women who undertook antiretroviral drug. The consecutive series of 178 HIV-seropositive women was enrolled in the Department of Obstetrics and Gynecology, Siriraj Hospital. All general information and laboratory results of the patients were recorded. Pap smears are obtained from the endocervix, cervical transformation zone and vagina by using a cotton tip stick and Ayre spatula, as described in the VCE technique. The patients were assigned into two groups, the AZT and non-AZT group. The comparison between the groups was calculated statistically.

It was found that 88 of 178 HIV-seropositive women (49.4%) undertook Zidovudine. The prevalence of abnormal Pap smear in HIV-seropositive women, who had an abnormal Pap smear, was 59.6 per cent. However, the prevalence of human papillomavirus infection detected by Pap smear was reported in 17 patients (9.6%). There was no difference between the AZT and non-AZT group statistically. There was a significantly higher probability of finding an abnormal Pap smear for cervical dysplasia in HIV-seropositive women who were infected with human papillomavirus compared to.

It is concluded that there is a higher risk of developing cervical dysplasia in HIV-seropositive women who carry the human papillomavirus.

Key word : Human Papillomavirus, Abnormal Pap Smear, Human Immunodeficiency Virus

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Human immunodeficiency virus (HIV) and human papillomavirus (HPV) are both sexually transmitted viruses, which have many risk factors in common. HIV became more prevalent in the 1980s, especially among intravenous drug users (IVDUs) and male homosexuals. Nevertheless, the number of HIV-seropositive women increased and the primary transmission mode of the virus in these women was defined as heterosexual transmission. It is also not surprising that many women with HIV infection also harbor HPV. Studies have shown a high rate of HIV infection among women with HPV-related disease[1,2]. On the contrary, as many as 42 per cent of HIV-seropositive women have experienced a variety of gynecological problems[3,4], and research findings suggest that HIV induced immunodeficiency was a predisposing factor for the development of cervical intraepithelial neoplasia (CIN) or cervical carcinoma by facilitating the expression of a causal agent[5-7]. The most common agent implicated in this process is the human papillomavirus[7,8].

Public health importance of research on the interaction between HIV and HPV infection with respect to cervical disease is suggested by the increased rate of cervical dysplasia, persistence and recurrence of cervical diseases and shorter survival for cervical cancer among women with HIV infection[9]. This link was highlighted in 1993 when invasive cervical cancer in the presence of HIV infection was added to the list of illnesses that define AIDS cases[10].

In Thailand, studies on HPV have not been well recognized, especially in the group of HIV-seropositive women. So, the authors established the present study to explore the prevalence of human papillomavirus (HPV) and abnormal Pap smear in HIV-seropositive women, particularly in HIV-seropositive women who undertook antiretroviral drugs, with the objective of informing gynecologists, using data from the Division of Gynecologic Infection and Sexually Transmitted Diseases, Siriraj Hospital.

MATERIAL AND METHOD

The study was conducted in Bangkok from 1996 to 1997, together with the HIV/AIDS Collaboration (HAC), a joint activity of the Thai Ministry of Public Health and the US Centers for Disease Control and Prevention.

The authors established a prevalence type sub-study of the main project concerning the usefulness of Zidovudine for prevention of mother to child HIV-transmission. 178 HIV-infected women were enrolled in the present study. They were recruited from the Division of Gynecologic Infection and Sexually Transmitted Diseases, Siriraj Hospital. Inclusion criteria for the subjects were documented HIV-infection without AIDS condition as defined by the US Centers for Disease Control and Prevention in 1987.

After post-test counseling, all eligible women were given information about the study and asked to provide written informed consent. It was emphasized that their participation in the study would in no way affect access to, or provision of, clinical care and that the participants could withdraw from the study at any time. All participants underwent a detailed interview dealing with their medical, social and drug use history, including history of their partners.

Smears were obtained from the endocervix, cervical transformation zone and vagina for Papanicolaou stain (Pap smear) by using a cotton tip stick and Ayre spatula, as described in the VCE technique, before any gynecological examination. The Pap smear was also used to diagnose HPV cervical infection in the subjects. The cytological report contained a description and could be interpreted as follows;

Grade 1: Within normal limits, findings essentially normal and no evidence of neoplasia.
Grade 2: Benign cellular change encompassing: infection (i.e. *Trichomonas vaginalis*, cellular changes associated with herpes simplex virus etc) and reactive changes (i.e. cellular changes associated with inflammation, radiation etc).
Grade 3: Epithelial cell abnormalities encompassing: mild dysplasia (CIN 1).
Grade 4: Epithelial cell abnormalities encompassing: moderate and severe dysplasia (CIN2 and CIN3/CIS).
Grade 5: Carcinoma encompassing: squamous cell carcinoma, adenocarcinoma or other malignant neoplasms.

An abnormal Pap smear was defined when the results of the cytological report ranged from grade 2 to 4.

In HIV-seropositive cases, viral load and CD 4 counts were determined in a local laboratory conducted by HAC.

Associations with demographic risk factors for HIV infection were determined. Based on antiretroviral drug use, the patients were assigned to two groups, the AZT and non-AZT group. The comparison between the groups was calculated statistically using the Student's *t*-test, Fisher's exact test, Chi-square test and Non-parametric test. (SPSS 10.0 for Windows and Epi Info Version 6, Centers for Disease Control and Prevention (CDC), Atlanta, GA). P-value < 0.05 was considered to be statistically significant.

RESULTS

Altogether 178 HIV-seropositive women were enrolled in the present study; and 88 (49.4%) of them were taking Zidovudine.

The characteristics of the 178 subjects are shown in Table 1. There were no statistical differences between the AZT and non-AZT groups (p-value > 0.05).

Concerning abnormal Pap smear in HIV-seropositive women, it was found that 106 (59.6%) of 178 patients had abnormal Pap smears ranging from grade 2 to 4. Almost the same patterns were shown in both groups (Table 2).

However, HPV infection was reported in 17 (9.6%) of 178 patients. When the subjects were divided into two groups, HPV infection was found in 12.5 per cent of the AZT and 6.7 per cent of the non-AZT groups. Even though, there was more HPV infection in the AZT group, it was not statistically different from the non-AZT group (p-value > 0.05) (Table 3).

The correlation between HPV infection and abnormal Pap smear is demonstrated in Table 4. There was a significantly higher risk of developing an abnormal Pap smear in subjects with HPV infection.

DISCUSSION

Nowadays, the HIV epidemic involving the heterosexual group is growing. A large number of new cases occurring in Asia involve child-bearing age women[11]. In Thailand, epidemiological studies have shown that female sex worker patronage is the leading HIV risk behavior for men, and it is widely presumed that most transmissions occurring in non sex workers is from their husbands or partners. Thus, women are at risk because of the risk behavior of their partners[11].

HPV, a virus of the Family *Papovaviridae* has received more interest during recent years. It infects only active proliferating epithelia of the skin and mucous membranes. Völter et al reported that at least 70 different HPV types have been identified[12].

Genital tract infection caused by HPV has become more common in women worldwide, especially in HIV-seropositive population. Some researchers reported that the HIV seropositive women who carry the cervical HPV infection have a higher chance of developing high-grade cervical lesions[13]. The histological appearance and natural history of HPV infection are largely determined by the HPV-DNA type [14]. Xi et al[15] reported in 2003 that HPV-16 and HPV-58 were the most frequently detected HPV types

Table 1. Demographic data.

Characteristic	AZT group (n = 88)	Non-AZT group (n = 90)	P-value
Age (mean ± SD)	24.8 ± 4.5	24.4 ± 4.8	0.63*
Age at first pregnancy (mean ± SD)	21.8 ± 3.9	21.8 ± 3.8	0.96*
Weight (mean ± SD)	49.6 ± 9.6	50.1 ± 7.2	0.70*
Family income less than 10,000 baht per month (%)	45.5	54.4	0.23**
Education higher than primary school (%)	36.4	42.2	0.42**
Viral load (copies/ml) (median, range)	26,951.5 (872-4,767,980)	25,952.5 (200-680,198)	0.89***
CD4 lymphocyte (cell/mm^3) (median, range)	411 (29-1,317)	444 (91-1,291)	0.71***

* Student's *t*-test
** Chi-square test
*** Non-parametric test

Table 2. Prevalence of abnormal Pap smear in the study subjects

Pap smear	Number of subjects	%	AZT group	%	Non-AZT group	%	P-value
Normal Pap smear	72	40.4	36	20.2	36	20.2	0.90*
Grade 1			36		36		
Abnormal Pap smear	106	59.6	52	29.2	54	30.4	
Grade 2			45		47		
Grade 3			5		4		
Grade 4			2		3		
Total	178	100	88	49.4	90	50.6	

* There was no statistical difference in prevalence of abnormal Pap smears in both groups as tested by Chi-square test (p-value > 0.05).

Table 3. Prevalence of HPV infection in the two groups detected by Pap smear.

Pap smear	AZT group (n = 88)	%	Non-AZT group (n = 90)	%	P-value
HPV-positive	11	12.5	6	6.7	0.19*
HPV-negative	77	87.5	84	93.3	

* There was no statistical difference in HPV infection between the two groups tested by Chi-square test (p-value > 0.05).

Table 4. Prevalence of HPV infection association with abnormal Pap smear.

Pap smear	Number of subjects	%	AZT group	%	Non-AZT group	%	P-value
Normal Pap smear	72	40.4	2	1.1	70	39.3	< 0.001*
Grade 1			2		70		
Abnormal Pap smear	106	59.6	15	8.5	91	51.1	
Grade 2			8		84		
Grade 3			5		4		
Grade 4			2		3		
Total	178	100	17	9.6	161	90.4	

* Chi-square test

that were strongly associated with the risk of cervical cancer.

Indeed, there are many techniques to detect human papilloma virus infection of the genital tract, such as visual inspection, cytological analysis, colposcopy, histological analysis (biopsy) and laboratory tests for HPV-DNA detection. Nevertheless, there is also a lack of consensus concerning the frequency and technique of cervicovaginal screening in women with HIV infection, which has led to wide variations in practice. At Siriraj Hospital, Papanicolaou stain (Pap smear) is used as the standard method for cervicovaginal screening, even for HIV-seropositive women. However, Chan et al[16] commented that routine screening with Pap smear does not appear to be a sensitive method for the diagnosis of HPV infection.

From the present study, there were no statistical differences in the demographic data between the AZT and non-AZT groups as shown in Table 1.

The present study has shown lower prevalence of HPV infection (9.6%) in genital tract of HIV seropositive cases compared to other reports. Minkoff et al[17] from New York in 1998 reported the prevalence of HPV infection in 73 per cent of HIV-sero-

positive cases. However, they used more sensitive technique to detect the viruses. (i.e. PCR amplification was used for the detection of HPV-DNA.)

It is interesting that the prevalence of abnormal Pap smears was the same whether the HIV-seropositive women undertook Zidovudine or not (Table 2). HPV prevalence was higher in the AZT group than the non-AZT group (12.5 *vs* 6.7%), however, there was no statistical difference.

However, the relationship between HPV infection and abnormal Pap smears (cervical dysplasia) was demonstrated significantly, which corresponds with other reports (Table 4)[17,18].

So the authors conclude that women who are HPV infected have a higher risk of developing cervical dysplasia. However, the subjects in the present study were limited to HIV infected women only. This relationship should hold true even if a study is performed on HIV seronegative subjects.

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ความสัมพันธุ์ระหว่างการติดเชื้อไวรัสฮิวแมน ปาปิโลมา และความผิดปกติของเซลล์ปากมดลูกในสตรีผู้ติดเชื้อเอ็ชไอวี โรงพยาบาลศิริราช

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พงษ์ศักดิ์ ชัยศิลป์วัฒนา, พบ, ขวัญจิตร เหล่าทอง, วทบ**

การวิจัยนี้มีวัตถุประสงค์เพื่อศึกษาถึงความสัมพันธุ์ของการติดเชื้อไวรัสฮิวแมน ปาปิโลมา และความผิดปกติของเซลล์ปากมดลูกในสตรีผู้ติดเชื้อเอ็ชไอวี โดยเฉพาะในผู้ที่ได้รับยาต้านเชื้อไวรัส ทั้งนี้สตรีผู้ติดเชื้อเอ็ชไอวี จำนวน 178 ราย ได้เข้ามารับการรักษาในภาควิชาสูติศาสตร์-นรีเวชวิทยา โรงพยาบาลศิริราช ผู้ป่วยจะได้รับการตรวจหามะเร็งปากมดลูกด้วยวิธี Pap smear ข้อมูลของผู้ป่วยเป็นข้อมูลที่ได้จากการสัมภาษณ์ ร่วมกับการส่งตรวจทางห้องปฏิบัติการ สตรีผู้ติดเชื้อเอ็ชไอวี จะถูกแบ่งเป็น 2 กลุ่ม คือผู้ป่วยที่ได้รับและไม่ได้รับยาต้านเชื้อไวรัสเอ็ชไอวี จากนั้นจึงนำมาวิเคราะห์ทางสถิติ

ผลการวิจัยพบว่าร้อยละ 49.4 ของสตรีผู้ติดเชื้อได้รับยาต้านเชื้อเอ็ชไอวี โดยมีอุบัติการณ์การตรวจพบการติดเชื้อไวรัสฮิวแมน ปาปิโลมาเท่ากับร้อยละ 9.6 และอุบัติการณ์การตรวจพบความผิดปกติของเซลล์ปากมดลูกในสตรีผู้ติดเชื้อเอ็ชไอวี เท่ากับร้อยละ 59.6 ทั้งนี้เมื่อเปรียบเทียบระหว่างกลุ่มสตรีผู้ติดเชื้อเอ็ชไอวี ที่ได้รับหรือไม่ได้รับยาต้านเชื้อเอ็ชไอวี ไม่พบว่ามีความแตกต่างอย่างมีนัยสำคัญทางสถิติ อย่างไรก็ตามสตรีผู้ติดเชื้อเอ็ชไอวี ที่ได้รับการตรวจพบเชื้อไวรัสฮิวแมน ปาปิโลมา มีโอกาสสูงกว่าอย่างมีนัยสำคัญทางสถิติที่จะตรวจพบว่ามีความผิดปกติของเซลล์ปากมดลูกร่วมด้วย

โดยสรุปสตรีผู้ติดเชื้อเอ็ชไอวี ที่ได้รับการตรวจพบเชื้อไวรัสฮิวแมน ปาปิโลมา มีความเสี่ยงที่จะพบความผิดปกติของเซลล์ปากมดลูกมากขึ้น

คำสำคัญ : ไวรัสฮิวแมน ปาปิโลมา, ความผิดปกติของเซลล์ปากมดลูก, ผู้ติดเชื้อเอ็ชไอวี

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