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Human Papilloma Virus and Associated Cervical Lesions in Women Co-infected with HIV

HIV ile Ko-enfekte Kadınlarda İnsan Papilloma Virüsü ve İlişkili Servikal Lezyonlar

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Abstract

Objective: Human papilloma virus (HPV) is one of the most important causes of cervical cancer, which is one of the AIDS-defining clinical conditions. In this study, it was evaluated the incidence of HPV and the cytopathological changes caused by HPV in the cervix, among human immunodeficiency virus (HIV)-positive women.

Methods: This study was conducted on HIV-positive women between 2010-2020. Patients were obtained cervical smear samples for HPV-DNA (PCR Roche-Cobas) analysis. Based on HPV test results, patients having one or both of the HPV 16 or 18 were designated as "HPV 16/18 positive". Patients with at least one of the other high-risk HPV types were termed as "Other HR HPV-positive."

Results: Twenty-two female patients were included in this study. Their mean age was 40.8 (range: 19-65) years. HPV subtypes were found as the following: HPV-16 in 1 patient (4.5%), HPV-18 in 3 (13.6%), and other HR-HPV in 9 patients (40.9%). In three individuals, HPV-18 co-existed with other HR HPV. The number of subjects with any type of carcinogenic HPV was 10 (45%). The cytological examination determined the presence of pre-cancerous lesions in five patients (22.7%), including atypical squamous cells of undetermined significance (ASCUS) in three (13.6%), and low grade squamous intraepithelial lesion (LSIL/CIN-1) and high grade squamous intraepithelial lesion (HSIL/CIN2-3) in one. Cervical lesions of all patients have regressed in the follow-up.

Conclusion: HIV-positive women have an increased rate of genital HPV infection and precancerous cervical lesions. Most infections in our study are caused by serotypes other than HPV 16 and 18 and all cervical lesions regressed in follow-up.

Keywords: Human papilloma virus, human immunodeficiency virus, cervical cancer, human papilloma virus 16, human papilloma virus 18

Öz

Amaç: İnsan papilloma virüsü (HPV), AIDS tanımlayıcı klinik durumlardan biri olan servikal kanserin en önemli nedenlerinden biridir. Bu çalışmada insan immün yetmezlik virüsü (HIV) pozitif kadınlarda HPV insidansının ve HPV'nin servikste neden olduğu sitopatolojik değişikliklerin değerlendirilmesi amaçlandı.

Yöntem: Bu çalışma HIV pozitif kadınlarda, 2010-2020 yılları arasında yapıldı. Hastalardan HPV-DNA (PCR Roche-Cobas) analizi için servikal yayma örnekleri alındı. HPV test sonuçlarına göre HPV 16 veya 18'den birine veya ikisine sahip olan hastalar "HPV 16/18 pozitif" olarak belirlendi. Diğer yüksek riskli HPV tiplerinden en az birisine sahip olan hastalar "diğer YR HPV pozitif" olarak adlandırıldı.

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Öz

Bulgular: Bu çalışmaya 22 kadın hasta dahil edildi. Ortalama yaş 40,8 (dağılım 19-65) idi. HPV alt tipleri; 1 hastada (%4,5) HPV-16, 3 hastada (%13,6) HPV-18 ve 9 hastada (%40,9) diğer YR-HPV olarak bulundu. Üç kişide HPV-18, diğer YR-HPV ile birlikte saptandı. Herhangi bir kanserojen HPV tipine sahip hastaların sayısı 10 (%45) idi. Sitolojik inceleme beş olguda (%22,7) kanser öncesi lezyonların olduğunu gösterdi. Bunlar arasında; üç hastada (%13,6), belirsiz öneme sahip atipik skuamöz hücreler (ASCUS), bir hastada düşük dereceli skuamöz intraepitelyal lezyon (LSIL-CIN1), bir hastada yüksek dereceli skuamöz intraepitelyal lezyon (HSIL-CIN2/3) saptandı. Takiplerinde tüm hastaların servikal lezyonları geriledi.

Sonuç: HIV pozitif kadınlarda, prekanseröz servikal lezyonların yanı sıra genital HPV enfeksiyonu oranı da yüksektir. Çalışmamızdaki enfeksiyonların çoğu HPV-16 ve 18 dışındaki serotiplerden kaynaklanmaktadır ve izlemde tüm servikal lezyonlar gerilemiştir.

Anahtar Kelimeler: İnsan papilloma virüsü, insan bağışıklık eksikliği virüsü, servikal kanser, insan papilloma virüsü 16, insan papilloma virüsü 18

Introduction

Human papilloma virus (HPV) infection represents one of the most common sexually transmitted infections globally, with a prevalence rate of 10.4% among women. Although its incidence varies from region to region (8-22.1%), the prevalence is highest among women under 35 years of age and declines with increasing age[1]. Although most HPV infections are asymptomatic and self-limiting, it is implicated as a leading cause of cervical cancers[2]. Until now, more than 100 types of HPV have been identified, and of these 40 were associated with cervical infections, and 15 with cervical cancer. Carcinogenic HPV subtypes have been defined on the basis of high or low risk of carcinogenicity. Types 16 and 18 represent high-risk subtypes accounting for nearly 70% of cervical cancers. Also, HPV subtypes 31, 33, 45, 52, and 58 are high risk (HR) viruses and responsible for approximately 19% of the cancers. Other HR subtypes, 35, 39, 51, 56, 59 are rarely associated with cervical cancer[3].

Studies from different geographical areas examining predisposing factors for HPV infection among HIV-positive women had identified several risk factors associated cervical lesions, including; being non-Caucasian, smoking 1 to 20 cigarettes per day, having more than one sexual partner within the last year, the co-existence of other sexually transmitted diseases and HIV-related parameters as CD4+ T cell number and anti-retroviral treatment[4].

Cervical cancer is one of the AIDS-defining clinical conditions. However, infection due to oncogenic HPV is the most important cause of cervical cancer, which exhibits an increased prevalence among HIV-positive women[5]. HPV infected HIV-positivewomen are more likely to develop persistent and recurrent lesionssuch as high grade squamous intraepithelial lesions (HSIL)[6,7]. Also, cervical intraepithelial neoplasm 3 (CIN3), *in situ* adenocarcinoma, and cervical cancer have been reported more commonly among HIV-positivewomen compared to HIV-negative women. Therefore, these women should be routinely screened for cervical cancer, abnormal results should be carefully followed up, and histologically documented pre-cancerous lesions should be treated[8]. In our country, efforts have been devoted to developing nationwide cancer screening programs using methods such as Papanikolaou (Pap) smear and HPV DNA assays[9].

This study assessed the incidence of HPV and the related cytopathologic lesions of the cervix among HIV-positive women followed up in our infectious disease unit.

Materials and Methods

This study was conducted on HIV-positive women followed up at our unit between 2010 and 2020. All women who agreed to participate in the study included. There were no other exclusion criteria. All patients provided written consent form and the study was approved by the Ethics Committee of İzmir Tepecik Education and Training Hospital (date: 25th Apr 2019, no: 2019/7-22). Patients were referred to the gynecology clinic, for obtaining cervical smear samples and HPV-DNA (PCR Roche-Cobas) analysis and typing. Pap smears were evaluatedcytologically according to the Bethesda Systemand histologically if necessary by a pathology specialist[10].

Based on HPV test results, patientshaving one or both of the HPV 16 or 18 were designated as "HPV 16/18 positive." Patients with at least one of the high-risk HR HPV types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82) were termed as "Other HR HPV-positive". Additionally, parameters such as CD4+ T cell counts and HIV viral load were evaluated.

Statistical Analysis

Descriptive statistics; were given as numbers and percentages for categorical variables, and as mean and standard deviation, median and interquartile range (IQR)

for numeric variables, depending on whether they fit the normal distribution or not. Pearson's chi-square or Fisher's exact test was used to compare categorical data with each other, Student's t-test was used if it fit normal distribution in comparison of numerical variables, and Mann-Whitney U test used when it did not. Analysis was performed using the Statistical Package for the Social Sciences 22.0 (IBM Corporation, Armonk, New York, United States) program, and a two-way p value <0.05 was considered statistically significant.

Results

Twenty-two female patients followed up in our unit were included. The mean age was 40.8 (range: 19-65) years and the mean first sexual intercourse age was 19.5 years (range: 12-41). Nine patients (41%) had more than one partner, with a mean partner number of 1.5. Six patients (27%) were smokers, and three had a positive family history of cancer, including one with cervical cancer. None of the patients were vaccinated against HPV. The median CD4+ T cell count was found as 768.5 (IQR: 601.7, minimum: 251-maximum: 1504) cells/mm^3. Viral load assays showed aHIV-RNA <50 copies/mL in 14, 50-1000 copies/mL in 2 and 1000-10000 copies/mL in 3 patients. The median duration of follow-up and treatment for HIV infectionwas 4 years (range: 0-11 y).

Cytological and molecular assessments were performed from Pap smear samples in all patients and biopsy samples were also collected if required. HPV subtypes were found asHPV-16 in 1 patient (4.5%), HPV-18 in 3 (13.6%), and other HR in 9 patients (40.9%). In three individuals, HPV-18 co-existed with other HR HPV. The number of subjects with anytype of carcinogenic (HPV 16, 18 and other HR types) HPV was 10 (45%). The mean age at first coitus was 18.3±4.5 in patients with HPV infection and 20±7.6 in patients without HPV infection and no statistically significant difference was found (p=0.601).

The cytological examination determined the presence of pre-cancerous lesions in five patients (22.7%), including atypical squamous cells of undetermined significance (ASCUS) in three (13.6%), and low grade squamous intraepithelial lesion (LSIL/CIN-1) and high grade squamous ıntraepithelial lesion (HSIL/CIN2-3) in one. Among three patients who had biopsy-sampling condyloma acuminata with LSIL, fibro-epithelial polyp, and HSIL were identified. One patient with HPV-16 was found not to have any pre-cancerous lesions, but all three patients with HPV-18 co-existing with other HR HPV types had pre-cancerous lesions (HSIL, LSIL, and ASCUS). Of these 3 cases, 2 underwent biopsy, showing similar findings. In the follow-up, the first HPV-18 and other HR co-existing patients with HPV who had HSIL had regressed to LSIL in one year. The second patient who had HSIL lesions underwent a loop electrosurgical excision procedure. Her cervical lesions turned benign in three years of follow-up. The cervical findings of the third patient with LSIL turned to normal spontaneously in two years.

The cytological examination in 6 patients having only other HR HPV types showed ASCUS in two. In the follow-up smear results turned normal in one year in both patients.

In patients with precancerous lesions, CD4+ T cell count was found to be higher (median 922 versus 764 cells/mm^3) but it was not found statistically significant (p=0.896). Four of the five patients with precancerous lesions had viral load data and their results were negative.

In patients that HPV could not be identified no cervical lesions were observed. Fourteen patients (63.6%) had a past history of genital infections (HSV-2 in 7, syphilis, and vaginal candidiasis in 3, *Trichomonas vaginalis* in 1). There was no statistically significant difference in the frequency of these infections in patients with and without HPV infection (p=1).

The patients with positive HPV DNA cervical Pap smear and biopsy results, also immunologic and virologic parameters are shown in Table 1.

Laboratory results and follow-up duration of the patients with negative and positive HPV DNA are given in Table 2.

Discussion

The risk of developing cervical cancer is 400 times higher with HPV-16 infection and 250 times higher with HPV-18 compared to uninfected women[11]. HIV-positive women have a 4.2 fold increased genital HPV infection compared to HIV-negative women. Furthermore, HIV-positive women are more likely to have high-risk genotypes other than HPV-16 and 18. These genotypes are responsible for LSIL and HSIL lesions, with a 5.4-fold increased risk of cervical cancer[5,6]. Following the genital HPV infection, the latency for developing cervical cancer is generally 10 years or longer. However, progression to cancer may be accelerated in some cases depending on the number of factors such as the type of HPV, immunosuppressive conditions such as HIV, other sexually transmitted diseases, parity, age at first birth, and cigarette smoking[12]. In our study, a genital infection was found in approximately half of the women, the most

Table 1. HPV DNA results, cervical lesions, CD4+ T cell and HIV RNA findings of the patients

Patient number	HPV 16	HPV 18	Other HR HPV	Smear results	Biopsy	Median CD4 cells/mm³	Minimum CD4 cells/mm³	HIV RNA copies/mL	HIV follow-up/years	HPV follow-up/years
1	**+**	-	-	Reactive and reparative changes	Fibroepithelial polyp	619	568	840	3	3
2	-	**+**	**+**	**HSIL (CIN-2/3)**	**LSIL (CIN-1) and Condyloma acuminata**	1224	570	Negative	1	2
3	-	**+**	**+**	**LSIL (CIN-1)**		922	893	Negative	4	3
4	-	-	**+**	Reactive and reparative changes		1056	340	Negative	5	1
5	-	-	**+**	**ASCUS**		1504	1400	Negative	5	2
6	-	-	**+**	**ASCUS**		280	916	Negative	9	2
7	-	-	**+**	Reactive and reparative changes		N/A	N/A	N/A	12	8
8	-	-	**+**	Reactive and reparative changes		859	659	Negative	1	1
9	-	-	**+**	Atrophic		394	43	8.060	1	1
10	-	**+**	**+**	**ASCUS**	**HSIL (CIN-2)**	251	201	N/A	9	4

HPV: Human papilloma virus, HIV: Human immunodeficiency virus, ASCUS: Atypical squamous cells of undetermined significance, LSIL: Low grade squamous intraepithelial lesion, HSIL: High grade squamous intraepithelial lesion

Table 2. Results of the patients with negative and positive HPV DNA

HPV DNA	Number of patients	HPV 16 (n)	HPV 18 (n)	Other HR HPV (n)	Smear results (n)	Biopsy (n)	Median CD4 cells/mm³	Minimum CD4 cells/mm³	Mean HIV RNA copies/mL	HIV mean follow-up/years
Negative	**12**	None	None	None	No precancerous lesions	None	764 (333-1329)	405 (242-1302)	3.697 (0-33.600)	3
Positive	**10**	1	3	9	ASCUS (3) LSIL (1) HSIL (1)	Condyloma acuminata with LSIL (1) Fibro-epithelial polyp (1) HSIL (1)	859 (251-1504)	570 (43-1400)	1.112 (0-8060)	5.2

HPV: Human papilloma virus, ASCUS: Atypical squamous cells of undetermined significance, LSIL: Low grade squamous intraepithelial lesion, HSIL: High grade squamous intraepithelial lesion

common being HSV-2. However, no significant difference was found between other genital infections and HPV. Although the age at first sexual intercourse was lower in women with HPV positivity, it was not found to be statistically significant. Similarly, in a study conducted in our country, no relationship was found between HPV positivity and current age, first sexual intercourse age, parity, and miscarriage[13].

In a study from Italy involving 321 HIV-positive patients, 50.2% of these subjects were found to have an HPV infection. While more than one genotype was detected in 35% of the

patients, 18% patients had genotype 16, 11% had genotype 58, 10% had genotype 5, 9% had genotype 45, 7% had genotype 18. CIN1, CIN2, and CIN3 were detected in 16%, 4%, and 1% of patients, respectively[4]. In our study, approximately half of our patients (10/22) were infected with any carcinogenicgenotype of HPV. The most frequently identified species were HR HPV, followed by co-existenceof HPV18 and HR HPV, where only one patient had HPV16.

According to studies in our country among HIV-negative women, HPV prevalence ranges between 6.1% and 80% depending on the geographical area, risk status, presence of pregnancy, and cervical smear results[13-16]. In contrast with our findings, the most common HPV types identified in these studies were genotypes 16 and 18. Contrary to the findings in this study, HPV 16 and 18 types were detected more frequently in other studies conducted in our country. This is because these studies were conducted on HIV-negative women and patients mainly with canceroral cervical findings.

The exact cause of the increasedprevalence and more aggressive course of HPV among HIV-positive women is not fully elucidated. It has been claimed that HIV proteins may damage the tight junctions between epithelial cells. Also, HIV-related immunosuppression is thought to prevent spontaneous clearance of HPV[17]. Even in the era of combined antiretroviral therapy (ART), HPV clearance among HIV-positive women is lower than those with HIV negative[17,18]. The reduced T cell count in infected individuals with HIV may lead to inefficient clearance of the oncogenic types of HPV[19]. In another study, it was found that HPV frequency was higher in HIV-positive women than seronegative women (42.8% vs. 13.4%), and persistent HPV shedding was increased in immunosuppressed individuals with lower CD4 counts[20]. In line with this, an association between low CD4+ T lymphocyte count and oncogenic potential of high-risk HPV genotypes other than HPV16 has been reported in women infected with HIV[21]. Even a moderate decline in CD4+ T cell count represents a risk factor for developing CIN 2/3 and cervical cancer, while ART use for more than 2 years may be protective against CIN[22]. Most of our cases were receiving ART, had a negative viral load, and high CD4+ T cell counts. Also, the identified HPV genotypes are associated with a lower risk of cervical cancer. Therefore, both the abovementioned factors and, takingsmear samples early may explain the absence of more advanced lesions such as cancer in our study population.

In our country, cervical cancer screening is free of charge and widely practiced. Cervical cancer screening has been included in the nationwide screening scheme as a part of the cancer screening program conducted between 2009 and 2015 by the Cancer Control Department, Turkish Ministry of Health. Based on the National Screening Standards for Cervical Cancer, women between 30 and 65 years should be screened every 5 years by taking smear samples and HPV DNA[23]. However, HIV-positive women should undergo screening twice yearly, and once yearly after that, if initial test results are negative[24].

HPV was detected in nearly half of the our patients and precancerous lesions were found in more than one-fifth (22.7%). International guidelines recommend vaccinating HIV-positive girls and young women[25]. Some vaccines confer cross-protection against serotypes that are excluded in the vaccine[26]. Since 2006, two-valent vaccines (genotypes 16, 18) and four-valent vaccines (genotypes 6, 11, 16, 18) have been used to prevent precancerous and dysplastic lesions associated with high-risk HPV genotypes. In 2014, nine-valent vaccine was granted approval by the Food and Drug Administration (genotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58) [27].

In a study conducted in Denmark, the prevalence of HPV and the frequency of infection more than one genotype was found to be higher in HIV-positive women than in the general population.

The most frequent HPV genotype identified in our study was another HR HPV. Therefore, vaccinesincludingother genotypes with HPV 16 and 18 should be offered to HIV-positive individuals[18,28].

In one study, the estimated protection by bivalent, 4-valent, and 9-valent vaccines was reported to be 19%, 33%, and 48%, respectively[4]. These vaccines are highly immunogenic among HIV-negative individuals, but their long-term efficacy and safety are not well known. It has been reported that the administration of vaccines after suppression of viral load may be more effective, with 1.74 to 3.05-fold higher antibody responses[5]. The data about the immunogenicity of HPV vaccines in immunosuppressed or HIV-positive individualsare limited. HPV vaccines administered in three divided doses have been reported to be safe in HIV-positive women, males, and children between 7 and 12 years of age. Antibody responses to HPV vaccine were found to be similar regardless of ART use in HIV-positive patients compared with HIV negative. However, no data are available on the

scheme involving two doses of bivalent or quadri-valent vaccines[5]. In our study, none of our patients were vaccinated against HPV. The high costs of HPV vaccines in our country represent a significant barrier to widespread vaccination.

Study Limitations

Our study has certain limitations; retrospective and single-center design, small sample size due to the small number of HIV-positive women, and absence of complete HR HPV genotyping.

Conclusion

In conclusion, HIV-positive women have an increased rate of genital HPV infection and precancerous cervical lesions. Most infections in our study are caused by genotypes other than HPV 16 and 18 and cervical lesions regressed in follow-up. Routine screening, following upand, improving the vaccination rates should be done to reduce the risk of cervical cancer, among HIV-positive women.

Ethics

Ethics Committee Approval: All patients provided written consent form and the study was approved by the Ethics Committee of İzmir Tepecik Education and Training Hospital (date: 25th Apr 2019, no: 2019/7-22).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: U.S., H.A.U., S.A., G.E., G.T., Design: U.S., H.A.U., S.A., G.E., G.T., Data Collection or Processing: U.S., H.A.U., S.A., G.E., G.T., Analysis or Interpretation: U.S., H.A.U., S.A., G.E., G.T., Literature Search: U.S., H.A.U., S.A., G.E., G.T., Writing: U.S., H.A.U., S.A., G.E., G.T.

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