The interrelation between HIV and condyloma acuminata high-risk strain

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Abstract

Objective The purpose of this study is to determine the relationship of high-risk HPV (HR-HPV) strain with IHC staining between HIV and non-HIV patients.

Methods This study is cross-sectional research that involved 41 CA patients who underwent a biopsy to obtain histopathological data. A consecutive non-random sampling technique was used to select the subjects. The subjects were divided into CA with HIV and CA with non-HIV, we divide the subjects with ELISA examination. The IHC staining was subsequently performed to determine the HR-HPV strain. The finding was interpreted based on immunoreactive cells.

Results The average age of the HR-HPV strains group was 31.20±16.87 years, and the average age of its negative strains was 33.19±12.41 years (p=0.931). HIV-positive patients were 5 (100%) with HR-HPV, yet none was found in HIV-negative. Conversely, 12 patients (33.3%) are HIV-positive patients with low risk (LR)-HPV and 24 HIV-negative patients (66.7%) with LR-HPV. Statistic results showed a significant relationship between HIV incidence and HR-HPV (p=0.005). Patients with negative HR-HPV have a 0.810 times lower risk of HIV than positive HR-HPV.

Conclusion This study demonstrated that negative HR-HPV was a protective effect of HIV. CA patients with HIV infection were examined for high-risk CA strains with IHC staining to help determine prognosis and therapy.

Key words
High-risk HPV strains; Human papillomavirus; Human immunodeficiency virus; Immunohistochemistry.

Introduction

Condyloma acuminata (CA) is a sexually transmitted infection (STI) that often appears globally.[1] Condyloma acuminata is caused by human papillomavirus (HPV) characterized by single or multiple lesions in the anogenital area. The lesions are subsequently followed by itching

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with vaginal discharge and bleeding in women.[1,2]

The data taken from several hospitals in Indonesia varies. Condyloma acuminata ranks first in the number of new STI incidents in the 2008-2011 period, accounting for 20.5 to 26% of all STI incidents at the IMS Polyclinic, RSUP dr. Cipto Mangunkusumo, Jakarta.[3] Similarly, CA KA was ranked first in IMS Polyclinic visits from 2015 to 2018 at RSUD dr. Moewardi, Surakarta. There were also 27 new train incidents (2.46%) at the dermatology and venerology polyclinic of RSUP Prof. Dr. RD Kandou, Manado, from January 2012 to

December 2012.[4]

More than 200 strains of HPV have been identified, and 40 strains caused skin and genital mucosa infections.[5] Based on the ability to induce intraepithelial dysplasia, HPV strains are divided into two types: low risk (LR) and high risk (HR).[6] Human papillomavirus strains 6 and 11 rarely cause cervical cancer. Thus, they can be classified as low-risk. Low-risk HPV infection is responsible for 90% of cases of CA.[7] On the other hand, HPV strains 16 and 18 are high-risk or oncogenic strains due to their strong association with cervical dysplasia that can develop into a malignancy. Infections involving this gene strain are found in up to 70% of squamous cell carcinoma (SCC) cases of the penis, vagina, cervix and oropharinx.[8]

Condyloma acuminata is mainly caused by HPV strains 6 and 11. However, it can also be caused by other HPV strains, such as strains 16, 18, 31, 33, which are generally identical to malignancy.[9] Human immunodeficiency virus (HIV) infection is an infection that causes a decrease in the immune system and a set of symptoms known as acquired immunodeficiency syndrome (AIDS).[10] Patients with untreated HIV will experience decreased immunity resulting in susceptibility due to infection by various pathogens, one of which is CA.[11] The interactions between HPV and HIV are complex. HIV-infected patients are susceptible to various types of HPV infection.[12]

Condyloma acuminate cases can generally be diagnosed based on clinical examination and patient history. If needed, additional examinations can also be carried out such as acetowhite, cytological and histopathological tests, colposcopy, immunohistochemical examination (IHC), in situ hybridization (ISH), HPV antigen detection, and HPV DNA detection by polymerase chain reaction (PCR).[1] CA clinical manifestations cannot be differentiated

between benign paraneoplastic and benign dysplastic lesions. Histopathological examination can confirm the diagnosis. IHC of anti-HPV antibodies in HPV lesions showed a sensitivity of 90.9% and specificity of 85.7%, with an accuracy rate of 88%.[13] HPV does not contain genes encoding for replication enzymes. They depend on the host cell for their replication. Replication of viral genes E6 and E7 lead to cellular expression of the oncoproteins E6 and E7 that disrupt the cell cycle.[14]

Ehehalt *et al.* study demonstrates for the first time that HPV18 E7 oncoprotein can be detected in cervical smears using PCR-based HPV typing.[15] Stiasni *et al.* showed that the E6 and E7 oncoproteins expressed in uterine cervical carcinoma and CIN III. Tissue carcinoma in situ can be easily detected by Immunohistochemistry.[16] Study of Arista *et al.* total of 13 female with CA were Nucleic acids amplification assays (Polymerase Chain Reaction) used to detect the HPV infection revealed mostly caused by HPV-11 (30,76%) and HPV-6 (23,07%) only 1 patient in this study caused by HPV 18.[17] Contrary our study examined the incidence of HIV infection associated with HR-HPV in CA through the IHC staining.

Based on the matters mentioned above, the purpose of this study was to determine the relationship between high risk KA strains with CPI staining strains 16 and 18 in patients with HIV infection and non-HIV infection, so that it can help determine that HIV infection is at risk of having high AC risk.

Methods

A cross-sectional analytical observational study was conducted at the Dermatology and Venereology Polyclinic, RSUD DR. Moewardi Surakarta from July to December 2021.

The inclusion criteria were: 1) All Patients aged >18 years diagnosed with condyloma acuminata; 2) predilection in the genital and anogenital regions willing to participate in research by signing informed consent. And the exclusion criteria was patients who have other genital malignancies.

A consecutive non-random sampling technique was used to select the subjects. The subjects were divided into CA with HIV and CA with non-HIV, we divided the HIV and non-HIV subjects with ELISA examination.

Examine the relationship of HR-HPV strains in CA with IHC staining strains 16 and 18 in HIV and non-HIV patients to help determine the prognosis and therapy of CA with HR-HPV strain.

This study used the Chi-square test and multivariate logistic regression analysis. The statistical tests mentioned before was conducted with Statistical Packages of Social Sciences (SPSS) version 22.0.

This study was conducted to determine the HR-HPV strain in CA patients. Specimens that came from CA patients were obtained by biopsy procedure. Histopathological examination and IHC staining were subsequently performed to determine HR-HPV strains in CA patients. Identification of HR-HPV strains was conducted based on the shape of immunoreactive cells using 100 times magnification through an Olympus CX 22 microscope RFS-1 model and a 5.0 megapixel Optilab CMOS camera. Anatomical Pathologists performed the interpretation of the IHC results through repeated readings.

First, for immunohistochemical analysis, we collect the history, clinical examination, and diagnosis of CA were carried out through the acetowhite test. In the other hand, we used a consecutive sampling technique for data collection in HIV Infection of CA, then the subjects were divided into CA with HIV and CA with non-HIV. After that, the treatment of excisional biopsy for patients with CA lesions was an injection of local anesthetic with 2% lidocaine HCL. Each patient's skin biopsy will be examined for HR-HPV strains. Finally, obtaining checks are performed by recording, documenting and analyzing data.

This study used the Chi-square test and multivariate logistic regression analysis. The statistical tests mentioned before was conducted with Statistical Packages of Social Sciences (SPSS) version 22.0. We considered $p<0.05$ as statistically significant.

This research uses informed consent; an explanation is made of the research and the risks to the research subject. If the subject understands and is willing to participate, the subject must sign the informed consent. All data generated in this research will be kept confidential and only be used for research and scientific purposes. The research was initiated after obtaining permission from the Research Ethics Commission at Dr. Hospital. Moewardi Surakarta Number: 564/V/HREC/2021.

Results

Based on the sample size calculation, 41 patients were diagnosed with CA and had a predilection for the genital and anogenital regions. Based on the study results regarding the characteristics of the research subjects, including gender, age, occupation, sexual orientation, region, and sexual partner (**Table 1**).

It was found that there were five male subjects (100%) in the group of HR-HPV positive strains, and no female subjects

Table 1 Characteristics of Research Subjects.

Characteristics	HPV strains		P-value
	HR-HPV	LR-HPV	
Gender (n/%)			0.086
Man	5 (100.0%)	22 (61.1%)	
Woman	0 (0.0%)	14 (38.9%)	
Age	31.20±16.87	33.19±12.41	0.748
Occupation			
Student	2 (40.0%)	4 (11.1%)	0.344
Private	1 (20.0%)	14 (38.9%)	
Laborer	1 (20.0%)	1 (2.8%)	
Entrepreneur	1 (20.0%)	9 (25.0%)	
IRT	0 (0.0%)	6 (16.7%)	
Civil Servant	0 (0.0%)	1 (2.8%)	
Farmer	0 (0.0%)	1 (2.8%)	
Journalist	0 (0.0%)	1 (2.8%)	
Sexual Orientation			0.367
Homosexual	3 (60.0%)	11 (30.6%)	
Heterosexual	2 (40.0%)	20 (55.6%)	
Bisexual	0 (0.0%)	5 (13.9%)	

were found. For the HR-HPV negative strains, 22 men (61.1%) and 14 women (38.9%), and gender was not significance associated with HR-HPV strain (p= 0.086). The average age in the HR-HPV group was 31.20±16.87 years, and the average group of LR-HPV was 33.19±12.41 (p=0.931). The HR-HPV group has the following occupations; 2 students (40.0%) and private occupations, laborers and entrepreneurs were 1 person each (20.0%). The LR-HPV group contains 4 students (11.1), 14 private workers (38.9%), 9 self-employees (25.0%), 6 housewives (16.7%), while laborers, employees, farmers and journalist have 1 patient each (2.8%) (p=0.344).

The group of HR-HPV found 3 homosexuals (60.0%) and 2 heterosexuals (40.0%). LR-HPV groups consist of 11 (30.6%) homosexuals, 20 (55.6%) heterosexuals, and 5 (13.9%) bisexuals (p=0.367). The data on the characteristics of the research subjects have homogeneously distributed data.

The relationship between the prevalence of HIV and high-risk strains The chi-square test was to determine the relationship between HR-HPV with IHC staining strains 16 and 18 in HIV and non-HIV patients.

Based on **Table 2**, there are 5 HIV positive patients (100%) and none HIV negative patients (0%) with HR-HPV. Contrarily, there are 12 patients (33.3%) with HIV positive patients and 24 (66.7%) HIV negative patients in the LR-HPV group. The p-value= 0.005 <0.05 and the Coefficient Contingency of 0.405. This means that there is a significant relationship between the incidence of HIV and HR-HPV (p=0.005 <0.05) with a reasonably strong relationship (Coefficient Contingency= 0.405). The risk estimate f*or cohort in HR-HPV* is negative with a 0.810 value, which means that patients with LR-HPV have a 0.810-fold lower risk of HIV than those with HR-HPV.

Discussion

The results showed a significant relationship between the incidence of HIV and HR-HPV, and there was a relatively strong relationship. This study is in line with the meta-analysis conducted by Liu *et al.* (2019), who showed that HIV infection is strongly associated with an increased risk of HPV prevalence, and the risk is negatively proportionate to CD4 count.[18] Another study carried in French Antilles and French Guiana found that abnormal cervical smear was found in 24% of high risk-HPV-negative women and 42% of high risk-HPV-positive women, respectively (p= 0.003).

Table 2 Chi-Square test used simple and multiple logistic regression.

		HPV Strains		P-value	CC Risk
		HR	LR		
HIV	Positive	5 (100%)	12 (33.3%)	0.005	0.405 0.810
	Negative	0 (0.0%)	24 (66.7%)		
Total		5 (100%)	36 (100%)		

Age, gender, sexual orientation: first used the simple logistic regression and variables with p < 0.250, include into the multiple logistic regression.
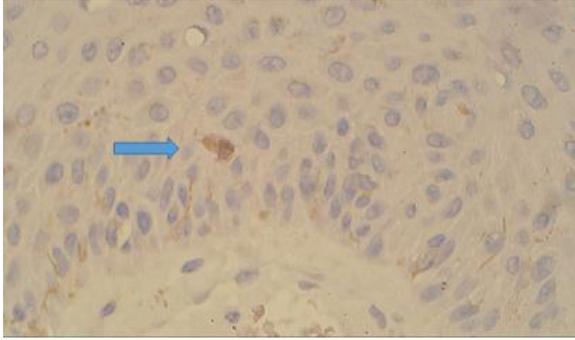
Figure 1 Immunohistochemical Results: Colored immunoreactive cells were seen brown (blue arrow) Showed Positive result for antibody E6 and E7 in HPV 16 or 18 describe more details about the arrow.

This showed that high risk HPV also significantly tend to attack HPV-positive women compared to HPV-negative women.[19] Tobian *et al.* (2013) reported that in HIV-positive men, HR-HPV prevalence was not linked to high-risk sexual behaviors. However, it is worth noting that the overall high HR-HPV prevalence among HIV-positive men (>74%) likely disguised any further link between HR-HPV and high-risk sexual activities. HR-HPV prevalence was linked to HIV infection, condom use, and an increased number of sexual partners in both HIV-negative and HIV-positive men during the course of their lives and in the previous year.[20] Infection with some strains of HPV can also cause cellular dysplasia that causes certain types of cancer, notably cervical cancer in women and penile or rectal cancer in men.[21] HPV strains 16 and 18 are high-risk strains to develop into a malignancy. Several studies have strengthened their role in developing cervical, anogenital and oral malignancies.[22]

The HPV, especially low-risk strain, will always be separated from the host cell DNA and replicated independently. In contrast to HR-HPV strains, they performed a genetic process where the viral DNA comes from the host cell's genetic material. The integration between the virus and host cell DNA causes imbalance and uncontrollable mobilization through E6 and E7 genes that promote oncoprotein transcription.[23] HIV patients are more likely to develop HPV infection, which is about 31-75%, with increasing disease duration and persistence. Patients with immunocompromised conditions have a higher risk of being infected with HPV, especially HPV strain 16, with larger and more numerous lesions and less responsive to therapy.[24] It can be concluded that there is a reasonably significant relationship between the incidence of HIV and HR-HPV.

Repeated CA were observed to be as common as 110 per 100,000 in females and 163 per 100,000 in males. Females' numbers peaked before 24 years of age, while males' levels surged between 25 and 29 years of age.[25] The risk factors for long-term persistent CA occur in immunosuppression patients, infection with HR-HPV strains, and elderly patients.[1,26]

CA can be seen on the scrotum, the shaft of the penis, and the tip of the penis in males. GA can also appear on the vulva, the vagina, or the cervix in women. GA can be found in the groin and around the anus in both men and women.[27] The clinical picture of CA varies, such as papules or lesions with granular papillae on the skin with mucoid appearance. The lesions initially appeared as small lumps with a diameter of 2 to 5 millimeters but can develop into large and dense masses.[1] A study stated that the ability of the virus to reproduce itself is limited to the basal cells of the skin tissue. The virus will pass through the epithelium of the skin and mucosa in a suitable cellular host then infects the basal keratinocytes of the epidermis. Areas affected by infection will be recognized by the spread of viral DNA characterized by lesions in the form of macules or plaques.[28]

The limitation of this study small sample and les variety of HR-HPV, In future research, it is expected to use a larger number of samples and

more varied HR-HPV strains.

Conclusion

There is a significant relationship between the incidence of HIV and the HR-HPV. These results indicate that condyloma acuminata patients with HIV infection should be examined for high-risk CA strains with IHC staining to help determine prognosis and therapy so that patient outcomes are also satisfactory.

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