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The Correlation Of Condyloma Acuminata On The Expression Of Protein Retinoblastoma (Prb) In Hiv Patients

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Abstract:
Background*: Condyloma acuminata (CA) is a sexually transmitted infection caused by several strains of Human Papillomavirus (HPV). The prevalence of CA worldwide is around 10-20% with the incidence continuing to increase. CA generally occurs in individuals infected with the Human Immunodefficiency Virus (HIV) and sexually active populations who are at high risk, such as men having sex with men. The risk of HIV transmission may also be increased in individuals with CA, and HPV infection is thought to accelerate HIV transmission. Individual with HIV who have low CD4 levels can increase CA proloferation. Protein retinoblastoma (pRb) has an important role in cell cycle control and is a marker of CA prognosis in its function of inhibiting the activity of the transciption factor E2F. Weak pRb expression leads to tumorigenesis, whereas HIV infection triggers inflammation and oxidative stress, and HPV disrupts the E7 cell cycle which can harm cellular pathways including pRb, altering normal cell cycle responses. This study aims to find the relationship between CA and pRb expression in HIV patients.*
Method*: This study used a cross-sectional analytical observasional design. Twenty-seven subjects were taken at the Dermatology and Venereology outpatient clinic at Dr. Moewardi General Hospital Surakarta Indonesia with a clinical and histopathological diagnosis of CA. The sampling method used was consecutive sampling. Immunohistochemistry was performed to examine pRb expression, while HIV status data was examined using the ELISA.*
Results*: Total of 11 subjects had pRb expression in the weak category and 16 in the moderate-strong category. The Chi-Square test carried out on sexual orientation found that there was a significant correlation with pRb expression (r= 0.474, p=0.005; p<0.05), while on CD4 count no significant correlation was found (r= 0.0351, p= 0.149) in CA patients with HIV.*
Conclusion:*there is a significant correlation between sexual orientation and pRb expression, but there is no correlation was found between CD4 count and pRb expression in CA patients with HIV.*
Keyword*:Condyloma acuminata, Human Immunodefficiency Virus, Human Papillomavirus*

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I. Introduction

Condyloma acuminata (CA) is a sexually transmitted infection (STI) with early clinical manifestations of growth as a skin-colored papule with a flat top that can develop into pink spot found in the anogenital area.[1]HPV strains of types 6 and 11, in particular, are common cause of CA in the anal.[2] Virus HPV menyebar melalui kontak seksual The HPV spreads through sexual contact.[3]Risk factors for CA include alcohol consumption, smoking, immonodefficiency, HIV/AIDS, a history of CA, and same-sex relations without a condom.[4] The prevalence of CA globally is around 10-20% and increases over time. CA became the main cause of patients visit to STI outpatient clinic at Dr. Moewardi General Hospital in 2021.[6]Clinical manifestations of CA can be vary, they can be flat lesions or have filiformic projection or papillomatosis.[7]Treatment of CA involves various methods depending on the progression of the disease, such as systemic or topical drugs, lasers, fulguration, and surgery.[8]Increases the risk of anogenital cancer, especially CA lesions with anal dysplasia as precursors of squamous carcinoma. The risk of HIV transmission is increased in individuals with CA, and HPV is thought to accelerate the transmission of HIV.[9,10]

Protein retinoblastoma (pRb) has an important role in cell cycle control and can be a marker of CA prognosis.[11]pRbis often identified in HPV infections and can be correlated with the type of HPV.[12,13]Patients with asymptomatic chronic HIV infection induce pRb as a mediator of apoptosis resistance in monocytes. In connection with protective autophagy and contribute to monocytes survival during immune activation and/or HIV viremia.[14]The lower CD4 level, the higher a person's risk of developing CA. Low CD4 count can also increase proliferation in CA.[4]

Anogenital contact is more frequently carried out by homosexual couples has a significantly 14-fold greater risk of HIV incidence than non-anogenital contact.[15]CA with HIV positive was also found to be influenced by a person's sexual orientation.[4] Sexual orientation was also found to be significantly correlated with the expression of tumor suppressor protein, one of which is pRb.[16]This study aims to determine the relationship between pRb expression in CA patients with HIV reactive status.

II. Methods

This is a cross-sectional analytical observational study to determine the relationship between pRb expression in CA patients with HIV reactive status. The research was carried out at 2 locations, namely Dermatology and Venereology outpatient clinic at Dr. Moewardi General Hospital, Surakarta, Indonesia for taking CA samples and the Anatomical Pathology Laboratory, Faculty Medicine, Sebelas Maret University for examining the pRb expression by immunohistochemistry (IHC). The research was conducted from June 2023 to August 2023. The study undergone analysis from ethic committee of Dr. Moewardi General Hospital Surakarta and it was proven by an ethical clearance from Health Research Ethics Commission number 1.525/VII/HREC/2023.

Research Design: Cross-sectional analytical observational study
Research Location: Dermatology and Venereology Outpatient Clinic Dr. Moewardi General Hospital Surakarta for taking CA samples. Immunohistochemistry examination of pRb was carried out at the Anatomical Pathology Laboratory, Faculty of Medicine, Sebelas Maret University.
Research Duration: June 2023-August 2023.
Number of samples: 27subjects.
Number of samples calculation: The sampling technique used in this research was consecituve sampling to select research subjects who met the inclusion and exclusion criteria.
Research sample and sample selection methods: The population of this study were condyloma acuminata patients who had been diagnosed clinically and histopathologically. Data regarding HIV status was examined using the ELISA method**.**
Inclusion criteria: subject aged > 18 years old with condyloma acuminata and reactive HIV. The CA lesion measuring < 10 cm and willing to carry out research by signing an informed consent. **Exclusion criteria:** subject who refused to participate in the study.
Methodology Procedure

Samples that met the qualifications for inclusion were explained about the procedures, objectives, and asked for informed consent to be signed. Anamnesis, clinical examination, and diagnosis of condyloma acuminata were carried out through physical examination and an excisional biopsy to find koilocyte cells on histopathological examination.

Excisional biopsy treatment was carried out on the CA lesion, and local anesthesia was injected with 2% lidocaine HCl. Each patient's skin biopsy will undergo an immunohistochemistry (IHC) pRb examination. Obtaining checks is carried out by recording, documenting, and analyzing data.

pRb expression was obtained through IHC examination, with positive results indicating pRb expression. The reading method uses the semiquantitative Allred Score method, namely that the final score is the product of the staining intensity score and the percentage of cells stained. The final result is a score of 0 = 0-1 (negative); score 1 = 2-3 (weak expression category); score 2 = 4-6 (medium expression category); and score 3 = 7-8 (strong expression category).

Analisis Statistik

Data analysis was carried out using the Chi-Square test. Analisis data dilakukan dengan menggunakan uji Chi-Square. Significance is determined by $p<0.05$. The data calculation technique used in this research uses SPSS version 22 computer software.

III. Results

This study obtained 27 CA subjects with reactive HIV status. Subject characteristics were assessed based on gender, age, occupation, education level, and marital status (Table 1). Men were the dominant subjects in this study (81.5%). The subjects were mostly aged 21–30 years (55.6%) with jobs as private employees

(51.9%), and there were also CA patients among students (11.1%) and college students (7.4%). The education level of the subjects was mostly high school (55.6%), with unmarried status (63.0%).

Tabel 1. Characteristic data of the subjects

Characteristic	n	%
Gender		
Male	22	81,5
Female	5	18,5
Age		
≤20 years old	3	11,1
21-30 years old	15	55,6
31-40 years old	5	18,5
≥41 years old	4	14,8
Occupation		
Labor	1	3,7
Housewife	1	3,7
College student	2	7,4
Trader	2	7,4
Student	3	11,1
Private worker	14	51,9
None	1	3,7
Self-employed	3	11,1
Education level		
Elementary school	5	18,5
Junior high school	5	18,5
Senior high school	15	55,6
Diploma	1	3,7
Bachelor	1	3,7
Marital status		
Not married yet	17	63,0
Married	6	22,2
Divorced	4	14,8

The study evaluated three variables: pRb expression, CD4 count, and sexual orientation (Table 2). The largest proportion of the research sample in sexual orientation was homosexual/bisexual (70.4%), while straight only (29.4%). The majority of CD4 count results were in the range of 200-500 cells/ul and pRb expression was moderate-strong (59.3%).

Table2. Variables in this study

Variable	n	%
Sexual orientation		
Heterosexual	8	29.6
Homosexual /Bisexual	19	70.4
CD 4		
CD4<200	9	33.3
CD4 200-500	15	55.6
CD4 >500	3	11.1
pRb expression		
Weak	11	40.7
Moderate-strong	16	59.3

Table3.Chi-Square tests

Variabel	pRb expression				r	p-value
	Moderate/strong		weak			
	n	%	n	%		
Sexual Orientation					0.474	0.005*
Heterosexual	8	50.0%	0	0.0%		
Homosexual/bisexual	8	50.0%	11	100.0%		
CD4					0.351	0.149
CD4<200	3	18.8%	6	54.5%		
CD4 200-500	11	68.8%	4	36.4%		
CD4 >500	2	12.5%	1	9.1%		

Keterangan : uji korelasi koefisien kontingensi; *signifikan pada p<0.05

According to the findings presented in Table 3, there exists a statistically significant asscociation (r= 0.474; p= 0.005) between sexual orientation and the expression of pRb, with significance level of p<0.05. The relationship between the two is moderate to strong (r = 0.474; r = 0.400 – 0.599). Individuals who identify as heterosexual exhibit moderate-strong expression of pRb, while those who identify as homosexual/bisexual tend to display weak expression of pRb.

IV. Discussion

The study exhibits a higher representation of male subjects compared ti female subjects. A study by Nareswari et al. in 2020 revealed that among 94 recently diagnosed patients with CA, there were notable gender disparities in the age distribution of CA patients (p = 0.014).[17]The anatomical structure of women differs from that of men. The occurrence of female social stigma in the context of genital inspections and the spontaneous regression observed in 30% of CA cases.can be attributed to immune responses that inhibit viral multiplication. Consequently, the frequency of visits by women with CA is compatatively lower that men. The majority of individuals with CA are withing the age range of 21 to 30 years old. This aligns with a study conducted by Puspawati et al. in 2018, which found that CA predominantly affects adults (47.31%) due to their advanced age and typical engagement in sexual activity.[18]At that age, the occurrence of CA is linked to heightened inquisitiveness and sexual attraction, hence it is advisable to consistently pursue information in diverse formats.[19]

The survey revealed that the predominant occupations for individuals with CA were private workers, self-employee, students, and college students. A study conducted by Jayadharma and Wiraguna in 2020 revealed a notable correlation between occupation and the rates of CA occurrence, with the majority of participants being employed in the private sector.[20]Private workers posses a greater amount of leisure time, sufficient financial resources, and wide social connections, both within and beyond their professional environment. The amount of education has a significant impact on an individual;s knowledge, attitude, and sexual behaviour, making it closely linked to occurrence of CA.[5]The majority sample in this study were not married yet. The prevalence of STI is influenced by marital status, as CA is more likely to occur in individuals who often change partners and engage in unsafe sexual practices. Homosexual and bisexual communities encompass individuals who engage in genito-anal sexual activity without relying on security measures, while also engaging in alternating sexual relationship with male partners, regardless of their sexual health status. This particular category is frequently observed withing unmarried populations.[21]

This study establish a correlation between sexual orientation and the expression of pRb, although the amount of CD4 did not exhibit a significant association with pRb expression. High Risk-Human Papillomavirus (HR-HPV) can induce degradation of pRb, specifically through the action of E7 HR-HPV proteins. HR-HPV like HPV 16 and 18 are linked to squamous lesion that have the potential to progress into carcinomas. On the other hand. HPV 6 and 11 are low risk-HPV (LR-HPV) and are the main causes of CA.[3,22]

HPV E7 exhibits a significant propensity to specifically target pRb, leading to degradation, while HPV E6 specifically targets P53.[23]Nevertheless, research examining the correlation between pRb and the oncogene HPV types E6 and E7 yielded inconclusive findings. This is because the mutation in question is either a point mutation or a synonymous mutation, which does not modify the amino acid composition or gene expression. Quantitative approaches like enzyme-linked immunosorbent assays (ELISA) or western blots are more accurate than semi-quantitative methods for measuring pRb expression. In stages III and IV, the expression of E7 is notably greater than that of pRb, but in stages I and II, the expression of HPV E7 is comparatively lower than that of pRb.[24]

Crocetto's study on the correlation between sexual orientation and the susceptibility to genital tumours yielded comparable findings. There is a strong correlation between sexual orientation and the expression of tumour suppressor proteins, including pRb. While without concrete evidence, some sexual behaviours significantly contribute to the development of CA. There is a significantly greater statistical prevalence of oral HPV infection among homosexual males, who are considered to be a heightened risk.[16]This study revealed that subjects who identify as homosexual/bisexual exhibit a weak of pRb expression in comparison to heterosexual subjects. Oral HPV infections are far more common among homosexual, who are all at high risk.[25] A study conducted at Dr. Sardjito Hospital in Yogyakarta, revealed that the prevalence of HIV-positive individuals was higher among men sex with men groups compared to heterosexuals and bisexuals. Additionally, only approximately 1.7% of these individuals had received HPV vaccination.[18]The low occurrence of this condition may serve as a foundation for both immunization and the inclination to seek medical attention for genital issues. Heterosexuals, who are perceived as culturally acceptable by the general population, exhibit a reduced level of awareness when it comes to undergoing regular hospitalization compared to homosexuals. Homosexuals couples typically tend to show a tendency to exert pressure and provide assistance in order to encourage the optimal utilization of healthcare services for their partners.[26]

This study could not identify a statistically significant association between CD4 count and pRb expression. This phenomenon may be attributed to subjects diagnosed with HIV who are undergoing antiretroviral therapy (ART) using lamivudine, nevirapine, or zidovudine. The ART study revealed that these medications had a contrasing impact on both HR-HPV and LR-HPV. It was suggested that ART has ability to inhibit HPV proliferation.[18]

This study demonstrated a propensity to decreased CD4 levels, suggesting a weak pRb expression (54.5%). The expression of RB and p21 genes, as well as the accumulation of autophagic markers LC3 and Beclin, are induced by monocytes exposed to HIV. Suppression of RB activity in monocytes infected with HIV leads to heightened susceptibility to apoptosis, thereby establishing the pivotal function of RB in the antiapoptotic appearance, as a defensive autophage, and its contribution to the survival of monocytosis during immunological activation and/pr HIV viremia.[14]

V. Conclusion

There is a significant correlation between sexual orientation and pRb expression, but there is no correlation was found between CD4 count and pRb expression in CA patients with HIV.

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