Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2023 Feb 03; 11(B):335-339.
https://doi.org/10.3889/oamjms.2023.11415
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Dermatology*

Relationship between Clusters of Differentiation 4 Count and Type of Human Papilloma Virus with Giant Condyloma Acuminata

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Edited by: Ksenija Bogoeva-Kostovska
Citation: Rohanda BA, Hutapea R, Nadeak K. Relationship between Clusters of Differentiation 4 Count and Type of Human Papilloma Virus with Giant Condyloma Acuminata. Open Access Maced J Med Sci. 2023 Feb 03; 11(B):335-339. https://doi.org/10.3889/oamjms.2023.11415
Keywords: Clusters of Differentiation 4 (CD4); Type of Human Papilloma Virus (HPV); Giant Condyloma Acuminata (GCA)
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Received: 19-Dec-2022
Revised: 10-Jan-2023
Accepted: 24-Jan-2023

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Condyloma acuminata (CA) is a sexually transmitted infection caused by the human papilloma virus (HPV). HPV infection is increasing in immunosuppressed patients which causes the development of CA lesions to be longer, recurrent, and larger. Clusters of differentiation 4 (CD4) count showed an association with the occurrence of giant condyloma acuminata (GCA).

AIM: The aim of the study was to determine the relationship between CD4 count and type of HPV with GCA.

SUBJECTS AND METHODS: This study was an analytic and observational study with a cross-sectional design with 20 human immunodeficiency virus-infected subjects (10 GCA and 10 non-GCA) selected using the consecutive sampling technique. CD4 examination using blood samples which were analyzed using fluorescence-activated cell sorting. CA lesions were taken using a shave biopsy technique and then the HPV type was examined using the polymerase chain reaction method.

RESULTS: The majority of the study subjects were male with GCA 7 people (41.2%). The most age group was 26–35 years old with GCA 6 people (66.7%). The education of the subjects was mostly senior high school with GCA 9 people (56.2%). The employment of the subjects was mostly service and sales personnel with GCA 4 people (57.1%). Based on the location of the GCA lesions, there were 4 people (57.1%) in the genital area and 6 people (46.2%) in the anal area. A total of 9 people (90%) with GCA had severe immunosuppression. The results of the analysis showed that there was a significant relationship between CD4 count and GCA ($p < 0.001$). The most common HPV type in GCA was HPV-11, amounting to 6 people (46.2%). The results of the analysis showed that there was no significant relationship between the type of HPV and GCA ($p = 0.275$).

CONCLUSION: There is a significant relationship between CD4 count with GCA and there is no relationship between type of HPV with GCA.

Introduction

Condyloma acuminata (CA) is a sexually transmitted infection (STI) caused by the human papilloma virus (HPV). CA can occur in both men and women, characterized by changes in mucosal and skin hyperplasia, especially in the anogenital area [1], [2]. Transmission of HPV occurs through sexual intercourse, either genitogenital, orogenital, or genitoanal. Thinner mucosa is a more susceptible area for virus inoculation than thicker keratinized skin, so microabrasion at the epithelial surface allows virions from the infected partner to enter the basal cell layer of the uninfected partner. Basal cells are the first site of HPV infection, so after inoculation through trauma, small HPV viruses will enter the basal epithelial cell layer [2].

HPV infection is increased in immunosuppressed patients, such as human immunodeficiency virus (HIV) infection, immunosuppressive therapy, and pregnancy. This condition will also cause the development of CA lesions to be longer, easy to recur, and larger (giant condyloma acuminata [GCA]). GCA, also known as Buschke-Lowenstein tumor (BLT), is a very rare clinical form of CA with a characteristic growth that invades the dermis and underlying tissue. GCA is usually benign, cauliflower-shaped lesions, located in the anogenital region with a diameter of more than 2.5 cm, and can reach a size of 10–15 cm. GCA was first described by Abraham Buschke and Lowenstein Ludwig in 1896 as a penile lesion similar to CA and squamous cell carcinoma with biologic characteristics and different histopathology [3], [4], [5], [6], [7], [8].

HPV types 6 and 11 are the most common in GCA. In addition, there were also multiple HPV types, namely, types 16 and 18, in lesions infected with HPV types 6 and 11, which were more likely to progress from CA to GCA. The finding of multiple HPV types is often associated with an infection that tends to be persistent. Persistent is defined as the same type being detected, at least on two examinations within 1 year. Persistent HPV infection is associated with the onset of clinical manifestations. The risk factors for the incidence of multiple HPV infections are HIV infection, more than

one sexual partner, and men who have sex with men (MSM) [9].

Clusters of differentiation 4 (CD4), also known as T-helper cells, are the coordinators of the immune response that protects the body against disease [10]. Normal CD4 count in adults ranges from 500 cells/μL to 1600 cells/μL. In the presence of infection and acute illness, the CD4 count will be lower [11]. CD4 count correlated with the level of immunosuppression, mild immunosuppression of CD4 350–499 cells/μL, moderate immunosuppression of CD4 200–349 cells/μL, and severe immunosuppression <200 cells/μL [12]. There is a decrease in Langerhans cells, T cell lymphocytes, macrophages, neutrophils, and natural killer cells in immunosuppressed CA patients, this causes changes in local immunity and occurs increased HPV infection in tissues [13].

Subjects and Methods

This study was approved by Ethics Commission in the Faculty of Medicine of Universitas Sumatera Utara. This study was an analytic observational study with a cross-sectional design, consisting of 20 HIV-infected subjects (10 people with GCA and 10 people non-GCA) at the Dermatology and Venereology outpatient clinic of Haji Adam Malik General Hospital and Universitas Sumatera Utara Hospital from January to May 2022. Subjects were selected by consecutive sampling. The samples of CA were collected by a shave biopsy technique, then followed by the examination of the HPV type using the polymerase chain reaction (PCR) method. CD4 examination using 3 mL of blood samples which were analyzed using fluorescence-activated cell sorting count. Inclusion criteria included patients diagnosed with GCA (CA with a diameter more than 2.5 cm) and non-GCA based on anamnesis and clinical examination, aged more than 18 years, and signed informed consent. Exclusion criteria were a history of coagulation disorders. The characteristics of patients including sex, age, education, employment, and CA location were recorded. The collected data were tabulated and presented as frequency and percentage. The relationship between CD4 and HPV type with GCA was statistically analyzed using the Chi-square test. If the Chi-square test conditions did not meet the criteria, the Fisher's exact test would be applied. However, if the two conditions did not meet the criteria, then the Kruskal–Wallis test would be applied. The results of statistical analysis were considered significant if $p < 0.05$.

Results

The HPV infection was detected in 20 HIV-infected subjects, 10 people with GCA and 10 people with non-GCA are shown in Table 1. A total of 17 people were male, 7 people (41.2%) had GCA and 10 people were non-GCA (58.8%). Meanwhile, 3 people (100%) were female who all had GCA. The results of the analysis using Fischer's exact test showed that there was no significant relationship between sex and GCA ($p = 0.211$).

Based on age group, a total of nine people aged 26–35 years old and 6 people (66.7%) of them with GCA. The results of the analysis using the Kruskal–Wallis test showed that there was no significant relationship between age and GCA ($p = 0.233$).

Based on education, there are 16 people with senior high school and 9 people (56.2%) of them with GCA. The results of the analysis using the Kruskal–Wallis test showed that there was no significant relationship between education and GCA ($p = 0.133$).

Based on employment, most of the subjects worked as service and sales personnel, amounting to seven people, and 4 people (57.1%) of them with GCA. The results of the analysis using the Kruskal–Wallis test showed that there was no significant relationship between employment and GCA ($p = 0.326$).

A total of seven people with genital lesions, 4 people (57.1%) with GCA, and 3 people (42.9%) non-GCA. Meanwhile, there were 13 people with anal lesions, 6 (46.2%) with GCA, and 7 (53.8%) non-GCA. The results of the analysis using Fischer's exact test showed that there was no significant relationship between lesion location and GCA ($p = 1.000$).

Table 1: The demographic characteristics patients

The demographic characteristics	GCA		p
	Yes	No	
Sex, n (%)			
Male	7 (41.2)	10 (58.8)	0.211[a]
Female	3 (100)	0	
Age (years old), n (%)			
17–25	3 (37.5)	5 (62.5)	0.233[b]
25–35	6 (66.7)	3 (33.3)	
36–45	1 (100)	0	
46–55	0	2 (100)	
Education level, n (%)			
Elementary and junior high school	1 (100)	0	0.133[b]
Senior high school	9 (56.2)	7 (43.8)	
Diploma/bachelor	0	3 (100)	
Employment, n (%)			
Professional	1 (25)	3 (75)	0.326[b]
Service and sales personnel	4 (57.1)	3 (42.9)	
Agricultural forestry and fishery workers	0	1 (100)	
Machine operators and assemblers	1 (33.3)	2 (66.6)	
Factory workers	1 (50)	1 (50)	
Housewife	3 (100)	0	
Lesion location, n (%)			
Genital	4 (57.1)	3 (42.9)	1.000[a]
Anal	6 (46.2)	7 (53.8)	

[a]Fischer's exact, [b]Kruskal–Wallis. GCA: Giant condyloma acuminata.

The results of the CD4 examination carried out on research subjects are presented in Table 2. Most of the subjects were found to have severe immunosuppression in 10 people, moderate immunosuppression in six people, and mild immunosuppression in one person. Meanwhile, three people were found with normal CD4 cells.

Table 3 shows the relationship between CD4 and lesion characteristics, from 10 people with severe immunosuppression there were 9 people (90%) with GCA lesions. The results of the analysis using the

Table 2: Characteristics of patients based on CD4

cell/µL	GCA		n=20
	Yes	No	
Normal	1 (33.3)	2 (66.7)	3
Mild immunosuppresion	0	1 (100)	1
Moderate immunosuppresion	0	6 (100)	6
Severe immunosuppresion	9 (90)	1 (10)	10

CD4: Clusters of differentiation 4, GCA: Giant condyloma acuminata.

Table 3: Relationship between CD4 and lesion characteristics

CD4, n (%)	GCA		p	RP
	Yes	No		95%IK
Severe immunosuppression	9 (90)	1 (10)	<0.001	9
Non-severe immunosuppression	1 (10)	9 (90)		(1.386–58.443)

[a]Chi-square. CD4: Clusters of differentiation 4, GCA: Giant condyloma acuminata.

Chi-square test showed that there was a significant relationship between CD4 levels and GCA lesions ($p < 0.001$) with a prevalence ratio value of 9 (95% CI 1.386–58.443) which means that subjects with severe immunosuppression will tend to be at risk of developing GCA lesions of 9 times greater than subjects with non-severe immunosuppression.

Table 4 shows the characteristics of HPV types from the results of the PCR examination carried out. Based on HPV type, there was one person with HPV-11 and HPV-16 who had GCA lesions, and two people with HPV-6 and HPV-11 who all showed positive GCA lesions. Meanwhile, from four people with HPV-6, only 1 person (25%) had GCA lesions and from 13 people with HPV-11, only 6 people (46.2%) had GCA lesions. The results of the analysis using the Kruskal–Wallis test showed that there was no significant relationship between the type of HPV and GCA lesions ($p = 0.275$).

Table 4: Characteristics of patients by type of HPV

Type of HPV, n (%)	GCA		p
	Yes	No	
HPV-6	1 (25)	3 (75)	0.275[a]
HPV-11	6 (46.2)	7 (53.8)	
HPV-6 and HPV-11	2 (100)	0	
HPV-11 and HPV-16	1 (100)	0	

[a]Kruskal–Wallis. HPV: Human papilloma virus, GCA: Giant condyloma acuminata.

Discussion

The majority of the subjects in this study were male with GCA totaling 7 people (41.2%). GCA is a rare case with an incidence of about 0.1% of the general population. It is more common in males and less reported in females [8], [14]. According to Purzycka-Bohdan *et al*. and Sandhu *et al*., GCA has an incidence of about 0.1% in the general population with a ratio of 2.7:1 in males to females [15], [16].

The largest age group is 26–35 years old with GCA amounting to 6 people (66.7%). Trombetta *et al*. showed that there was no difference in age range with the incidence of GCA ($p = 0.44$), the age range of GCA patients was 24–77 years old with a mean age of 43.9 years old (42.9 years old for men and 46.6 years old for woman) [17].

The majority of research subjects had a senior high school with a GCA of 9 people (56.2%). Research by Jayadharma et al. based on a study of 58 CA patients from 2011 to 2015 showed that the majority of CA patients had secondary education level (85% of patients) [18]. In contrast, the study by Silvia et al. regarding the relationship between education level and the incidence of CA in 71 CA patients showed a significant relationship ($p = 0.009$) where the majority of CA patients (49.3%) had low education [19]. Low education will affect a person's knowledge, attitudes, and sexual behavior so the tendency to have unsafe sex will be more significant [20].

The most employment is service and sales personnel with GCA amounting to 4 people (57.1%). Research by Silvia *et al*. in 102 patients with CA also showed that most patients with KA had private sector worker/service and sales (32.4%) followed by patients who did not work/housewife (23.5%). The study also showed that there was a significant relationship ($p = 0.03$) between employment and the incidence of condyloma acuminate [21]. The large number of CA patients from private sector workers may be due to the fact that they have a lot of free time, sufficient income, and good relationships in the work environment and outside of work. The research of Jayadharma *et al*. said that the customers of commercial sex workers are mostly private sector workers, this may be related to the high risk of STIs and CA in this group [18].

Based on the location of the lesions, 4 people (57.1%) with GCA had lesions in the genital area and 6 people (46.2%) with GCA had lesions in the anal area. The most frequently affected sites in male are the penis (81–94%) and in female the vulva (90%). The second most common location is in the perineal area in both males and females [14], [22].

A total of 9 people (90%) with GCA had severe immunosuppression. In Meghana's study, the most common viral infection found in immunosuppressed patients was HPV infection which was seen in 11 patients (7.69%). The average CD4 count of patients infected with HPV was 143.73/mm^3 (with a range of 78–215/mm^3). Nine patients with HPV were in the stage of severe immunosuppression. There were eight patients who had anogenital CA and one patient with GCA. The results of the analysis from a study by Megana regarding HPV infection with an average CD4 count in immunosuppressed patients with $p = 0.009$. This suggests that the prevalence of HPV infection in immunosuppressed (HIV positive) patients increases with decreased CD4 cell count [11].

Characteristics of the most common type of HPV in study subjects with GCA were HPV-11, amounting to 6 people (46.2%). Cong *et al*. conducted a correlation study of HPV types and clinical features in patients with CA found a single infection of HPV-6 in 31

people (38.7%) and HPV-11 in 29 people (36.3%), as well as multiple infections caused by HPV-6, HPV-11, HPV-16, HPV-18, and/or HPV-31 as many as 20 people (25%). Statistical analysis showed that multiple HPV infections resulted in greater CA formation (GCA), higher recurrence rate, longer disease course, and poorer prognosis [23].

Conclusion

There is a relationship between CD4 count with GCA and there is no relationship between the type of HPV with GCA.

Acknowledgments

We would like to express gratitude to the Head of the Department of Dermatology and Venereology of the Faculty of Medicine Universitas Sumatera Utara, Haji Adam Malik General Hospital, and Universitas Sumatera Utara Hospital.

Author Contribution

All authors have contributed to this research process, including preparation, data gathering, analysis, drafting, and approval to publish this manuscript.

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