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Clinical Characteristics of Anogenital Warts Among Patients Attending Genitourinary Medicine Clinic Hospital Kuala Lumpur Between 2015 and 2020

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Abstract

Background

Anogenital human papillomavirus (HPV) is the most frequent reported sexually transmitted infection in the world. We aim to describe the local demographic data and the clinical characteristics of anogenital warts (AGWs).

Methods

This is a retrospective study on all patients with AGWs who attended the GUM clinic between 2015 and 2020. Data was obtained from case notes and further analysed.

Results

A total of 935 patients with AGWs attended the GUM clinic between 2015 and 2020. The mean age was 30.4 years (range 12-84). The male to female ratio was 2.35:1. Majority were Malaysian (97%). Majority of the Malaysian were Malays (61.5%) followed by Chinese (27.7%) and Indian (8.9%). About 5.6% had a history of substance abuse. While the majority (57.9%) were heterosexual, 34.8% were homosexual and 6.4% were bisexual. About 59.8% had more than one sexual partner. A quarter (25.6%) was infected with the human immunodeficiency virus. The most frequent site of AGWs in males was the perianal area (52.6%), followed by the penis (45.7%), and with a fifth of them having lesions at multiple sites. For female patients, the most frequent site of AGWs was the posterior fourchette (45.2%) followed by the labia minora (33%) with 46.6% had involvement at multiple sites. Approximately 17.6% had other concomitant sexually transmitted infections. Local treatment application used included cryotherapy (86.4%), podophyllin (35.3%), tri-chloroacetic acid (26.8%) and imiquimod (2.6%). About 41.5% required combination of these modalities. Nearly 6.2% experienced recurrence. About 2% required surgical intervention.

Conclusions

AGWs was more commonly observed in male. The most frequent site of involvement was perianal for male (52.6%) and posterior fourchette in female (45.2%).

Key words: *Sexually transmitted infections, anogenital warts, Human Papilloma Virus, Human Immunodeficiency Virus*

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Introduction

Anogenital human papillomavirus (HPV) is the most frequently reported sexually transmitted viral infection in the world.[1] HPV 6 and 11 account for the majority of anogenital wart

(AGWs) cases and are highly infectious; approximately 65% of individuals with an infected partner develop AGWs within 3 weeks and 8 months.[2] Recent prospective studies reported that the median time between infection with HPV types 6 or 11 and the development of AGWSs was 11 to 12 months among males and 5 to 6 months among young females.[2] The transmission are predominantly through oral, anal and genital sexual contact, and, in rare instances, through vertical transmission and autoinoculation.[2] AGWs were strongly believed to be associated with high sexual partner numbers and unprotected sexual intercourse. This diagnosis was more common in men who have sex with men (MSM) and in women reporting sex with women.[1,2]

Four distinct sub-types of AGWs have been described which include condylomata acuminata (pointed warts), flat/macular lesions, papular, and keratotic lesions.[3] The first two sub-types are mainly found on moist, non-keratinized epithelia, while the latter two are usually present on keratinized epidermis.[3] They manifest as visible lesions, namely as single or multiple papules on the vulva, perineum, perianal area, vagina, cervix, penis, anus, scrotum and urethra.[3] Clinical symptoms may include pruritus, burning, vaginal discharge and bleeding. In rare cases, AGWs can be associated with malignant lesions, namely Buschke Lowenstein tumours.[3] Although AGWs do not usually result in major immediate morbidity or mortality, the psychological morbidity and very substantial healthcare costs is significant.[4]

This study aims to describe the local demographic data and the clinical characteristics of AGWs at Genitourinary Medicine Clinic, Department of Dermatology, Hospital Kuala Lumpur (HKL).

Materials and Methods

This is a retrospective study on all patients with AGWs attended GUM clinic, HKL between 1st July 2015 and 30th June 2020. Information including demographics, clinical features, human immunosuppressive virus (HIV) status, co-morbidities, co-infections, treatment durations, treatment modalities and recurrent rate was recorded into data collection form. Data collected was further analysed using SPSS version 21.

Results

A total of 935 patients with AGWs attended the GUM clinic, HKL between 2015 and 2020. A quarter (25.6%) of them was infected with the human immunodeficiency virus (HIV). The demographic data is shown in Table 1. The mean age of all the patients at presentation was 30.4 years (range 12-84), with a significant younger mean age among those infected with HIV. Majority of the patients (55.8%) were in the age group between 20-29 years. The male to female ratio was 2.35:1. More than 98% of those infected with HIV were male. Majority were Malaysians (97%) whereby 61.5% were Malays, followed by Chinese, (27.7%) and Indian (8.9%).

While majority (57.9%) were heterosexual, 34.8% were homosexual and 6.4% were bisexual. Interestingly, 80.3% of those infected with HIV were homosexual (vs non-HIV 19.1%, $p<0.0001$). A significant higher number of patients infected with HIV engaged casual sex partner (71.1% vs 28.3%, $p<0.0001$). About 59.8% had more than one sexual partner 6 months prior to presentation and it was significantly higher among HIV infected patients (83.3% vs 51.7%, $p<0.0001$). Fifty-two patient (5.6%) were documented to have substance abuse. About 17.6% had other concomitant sexually transmitted infections. Except chlamydial infection, the rate of syphilis, gonorrhea and herpes genitalis were significantly higher among those infected with HIV. Seventy females (25% of all female patients), all non-HIV infected, were pregnant at presentation. Furthermore, three patients (0.3%) had active malignancy and were undergoing anti-cancer treatment at presentation.

Table 1: Demographic characteristics of 935 patients attending GUM clinic Hospital Kuala Lumpur with anogenital warts

Characteristics		**Total**	**HIV status**		
		n = 935 (%)	**Positive** *n= 239 (%)*	**Negative** *n=696 (%)*	***p***
Gender	Male	656 (70.2)	235 (98.3)	421 (60.5)	**<0.0001**
	Female	279 (29.8)	4 (1.7)	275 (39.5)	
Mean age in years (range)		30.4 (12-84)	28.3 (15-68)	31.2 (12-84)	**<0.001**
Age group in years, n (%)	<20	32 (3.4)	9 (3.8)	23 (3.3)	**<0.001**§
	20-29§	**522 (55.8)**	**158 (66.1)**	**364 (52.3)**	
	30-39	258 (27.6)	52 (21.8)	206 (29.6)	
	40-49	61 (6.5)	10 (4.2)	51 (7.3)	
	50-59	37 (3.95)	8 (3.3)	29 (4.2)	
	60-69	17 (1.8)	2 (0.8)	15 (2.2)	
	>70	8 (0.85)	0 (0)	8 (1.1)	
Ethnicity, n (%)	Malay	558 (59.7)	141 (59.0)	417 (59.9)	**0.02**
	Chineseφ	**251 (26.8)**	**78 (32.6)**	**173 (24.9)**	
	Indian	81 (8.7)	10 (4.2)	71 (10.2)	
	Others (Bumiputera Sabah, Sikh)	17 (1.8)	7 (2.9)	10 (1.4)	
	Foreigner	28 (3.0)	3 (1.3)	25 (3.6)	
Sexual orientation, n (%)	Heterosexual	541 (57.9)	15 (6.3)	526 (75.6)	**<0.0001**¶
	Homosexual¶	**325 (34.8)**	**192 (80.3)**	**133 (19.1)**	
	Bisexual	60 (6.4)	28 (11.7)	32 (4.6)	
	Missing data	9 (1)	4 (1.7)	5 (0.7)	
Type of sexual partners, n (%)	**Casual**φ	**367 (39.3)**	**170 (71.1)**	**197 (28.3)**	**<0.0001**φ
	Regular	239 (25.6)	52 (21.8)	187 (26.9)	
	Spouse	233 (24.9)	3 (1.3)	230 (33.0)	
	Sex worker	24 (2.56)	1 (0.4)	23 (3.3)	
	More than 1 type	48 (5.13)	4 (1.6)	44 (6.3)	
	No partner	24 (2.56)	9 (3.8)	15 (2.2)	
Number of patients with 2 or more partners in the past 6 months, n (%)		559 (59.8)	199 (83.3)	360 (51.7)	**<0.0001**
Number with documented substance abuse, n (%)		52 (5.6)	13 (5.4)	39 (5.6)	0.94
Concomitant sexually transmitted infections (STI), n (%)	Syphilis	83 (8.9)	59 (24.7)	24 (3.4)	**<0.0001**
	Gonorrhoea	44 (4.7)	18 (7.5)	26 (3.7)	**0.02**
	Herpes genitalis	25 (2.7)	12 (5.0)	13 (1.9)	**0.02**
	Chlamydial infection	24 (2.6)	3 (1.3)	19 (2.7)	0.29
	Multiple other STI*	18 (1.9)	16 (6.7)	2 (0.3)	**<0.0001**
Comorbidities, n (%)	Pregnancy	65 (7.0)	0 (0)	65 (9.3)	-
	Diabetes mellitus	50 (5.3)	4 (1.7)	46 (6.6)	<0.001
	Pregnant with diabetes mellitus	5 (0.5)	0 (0)	5 (0.7)	-
	Malignancy	3 (0.3)	0 (0)	3 (0.4)	-
	Others	33 (3.5)	4 (1.7)	29 (4.2)	-

HIV – human immunodeficiency virus; * including hepatitis B and hepatitis C viruses

Table 2: Clinical Characteristics and treatments of anogenital warts (AGWs) in 935 patients attending GUM clinic, Hospital Kuala Lumpur

Characteristics		**Total** *n = 935 (%)*	**HIV status**		
			Positive *n= 239 (%)*	**Negative** *n=696 (%)*	***p***
Distribution of AGWs in men,	***Total***	***656***	***235***	***421***	
	Perianal	345 (52.6)	206 (87.7)	139 (33.0)	**<0.0001**
	Penis	300 (45.7)	38 (16.2)	262 (62.2)	<0.0001
	Scrotum	67 (10.2)	10 (4.3)	57 (13.5)	<0.0001
	Intra-anal	14 (2.1)	47 (20.0)	20 (4.8)	**<0.0001**
	Intra-urethral	11 (1.7)	2 (0.9)	16 (3.8)	0.02
	Mon pubis	1 (0.2)	0 (0)	1 (0.2)	-
	Multiple sites	135 (20.6)	66 (28.1)	69 (9.9)	**0.0002**
Distribution of AGWs in women,	***Total***	***279***	***4***	***275***	
	Posterior fourchette	125 (44.8)	0 (0)	125 (45.4)	-
	Labia minora	92 (33,0)	3 (75)	89 (32.4)	0.11
	Labia majora	80 (28.7)	3 (75)	73 (26.5)	0.07
	Clitoris	88 (31.5)	0 (0)	88 (32.0)	-
	Perineum	7 (2.5)	0 (0)	7 (2.5)	-
	Mons pubis	1 (0.4)	0 (0)	1 (0.4)	-
	Urethra	1 (0.4)	0 (0)	1 (0.4)	-
	Vagina	29 (10.4)	0 (0)	29 (10.5)	-
	Cervix	1 (0.4)	0 (0)	1 (0.4)	-
	Anus	6 (2.2)	0 (0)	6 (57.1)	-
	Multiple sites	130 (46.6)	3 (75)	127 (46.2)	0.30
Treatment provided	Cryotherapy	808 (86.4)	214 (89.5)	594 (85.8)	0.09
	Podophyllin	330 (35.3)	107 (44.8)	223 (32.0)	**0.0004**
	Tri-chloroacetic acid	251 (26.8)	90 (37.7)	161 (23.1)	**<0.0001**
	Imiquimod	24 (2.6)	5 (2.1)	19 (2.7)	0.62
	Combined modalities	388 (41.5)	131 (54.8)	257 (36.9)	**<0.0001**
Number who improved with treatment provided, n (%)		717 (76.7)	176 (73.6)	541 (77.7)	0.20
Number who required surgical intervention, n (%)		17 (1.8)	6 (2.5)	11 (1.6)	0.37
Mean number of treatments (range)		3.84 (0-62)	5.21 (1-62)	3.38 (0-28)	**<0.001**
Mean duration of treatment received in months (range)		2.16 (0-26)	3.09 (0-26)	1.84 (0-19)	**<0.001**
Recurrence within 6 months, n (%)		58 (6.2)	14 (5.8)	44 (6.3)	0.82
Lost to follow up		417 (44.6)	121 (50.6)	296 (42.5)	**0.03**

HIV – human immunodeficiency virus

The characteristics of AGWs and type of treatments provided are shown in Table 2. The most common site of AGWs in males was perianal (52.6%) followed by warts at penis (45.7%) and 20.6% had lesions at multiple sites. Interestingly, HIV infected male patients had a significant higher rate of AGWs at perianal and intra-anal region, with nearly 30% of them had involvement at multiple sites. For female patients, the most frequent site of AGWs was posterior fourchette (44.8%) followed by labia minora (33%) and about 46.6% had involvement of multiple sites. Biopsy was performed in 5 patients (0.5%) and they showed condylomata acuminata, with no dysplasia or carcinoma.

Local ablative treatment provided included cryotherapy (86.4%), podophyllin (35.3%), tri-chloroacetic acid (26.8%) and imiquimod (2.6%). About 41.5% required combination of these modalities and the rate was significantly higher rate among those infected with HIV (54.8% vs 36.9%, *p<0.0001*). Majority of our patients (76.7%) improved with these treatment modalities. The mean number of treatments was 3.84 with a range of 0-62. Patients who had very large lesions (2%) that were not suitable for local ablative treatment were referred for surgical intervention. The mean duration of treatment was 2.16 months with a range of 0-26 months. The duration and number of treatments for AGWs with concurrent HIV infected patients were significantly higher (both *p<0.001*). The overall rate of lost to follow up was high at 44.6%, higher among those infected with HIV. There were 126 patients (13.5%) lost to follow up after the first visit itself. Nearly 6.2% experienced recurrence with the rates were similar between those infected with HIV and without HIV.

Discussion

Previous audits done in Hospital Kuala Lumpur showed that AGWs are one of the most common sexually transmitted infections (STIs) encountered in GUM clinic as shown in Table 3.[5,6,7] A 10-year retrospective study on changing pattern of sexually transmitted infections in Hospital Kuala Lumpur showed that there was an overall decrease in bacterial STIs but an increase in viral STIs (genital warts, genital herpes and HIV).[5] In the United Kingdom, the number of genital warts in 2004 showed a 32% increase compared to 1995.[3] AGWs are a common manifestation of an HPV infection, particularly among young men and women. The prevalence of AGWs was estimated to range between 0.13% and 0.20% typically in most studies.[2]

Most of our local studies showed a male predominance in STI acquisition and sexual experience.[5,6,8] Multiple partner behaviour was found to be significantly associated with male gender.[8] Our data is similar to other countries (Table 4) whereby there was a male predominance for anogenital warts.[2,9,10,11] One of the reasons stated in some studies is that males who initially present with symptoms usually seek consultations with urologists or dermatologists whereas females routinely visit gynaecologists. The specialty of the physicians most frequently performing the initial diagnosis of AGWs varies depending on the healthcare system of individual countries, which could contribute to the differences in reported AGWs among genders.[2]

The most common age group presenting with warts was from 20 to 29 years and this was also observed in other reports worldwide (Table 4).[2,9-12,13-22] This age group is more sexually active and has a higher risk of behavioural vulnerability to acquiring STIs given the number of sexual partners. There are also more frequent partner changes compared to the older group. Another study found that anogenital wart incidence peaked among younger males due to high-risk sexual behaviour; this peak corresponded to new partner acquisition as well.[2] In the United States the median age of those with genital warts was 31.3 years among men who reported having sex only with women and 33.2 years among men who have sex with men (MSM)[10] and the mean age group in our cohort is 30.4.

AGWs was also reported to be higher among men who have sex with men (MSM) and in women reporting sex with women.[12,23] In Thailand the rate of human immunodeficiency virus (HIV) infection among those with anogenital warts was 15%.[13] Our data, however, showed a much higher rate of HIV in those with AGWs at 25.6%. The Genitourinary clinic, Hospital Kuala Lumpur is the one of the main referral centres for treatment of anogenital warts in HIV infected patients from health clinics around the vicinity of Kuala Lumpur and Selangor. This is because we provide ablative treatments.

AGWs are strongly associated with multiple partners and unprotected sex. Additional risk factors include the use of oral contraceptives,

Table 3: Comparison of clinic-epidemiological trend on anogenital warts (AGWs) in Genitourinary Medicine Clinic, Hospital Kuala Lumpur from 1995-2017

Study	Study year	n	% of AGWs among of all sexually transmitted diseases	Age group with highest frequency of AGWs or Mean age in years
Lim et al.[5],2007	1995-1999	171	5.43	30-49
	2001-2005	301	10.35	20-39
Hariyadurai et al.[6], 2019	2015-2016	389	30.2	32.09 ± 12.080
Krishnasamy et al.[7], 2019	2013-2017	273	43.2	31.2

Table 4: Comparison of clinic-epidemiological studies on anogenital warts in other countries

Author, year, country	**n**	**Male to female ratio of anogenital wart**		**Mean Age in years or most frequently affected age group**	**HIV (%)**	**Most frequent affected site**	**Treatment modalities used**
		Male	**Female**				
Tan et al, 2022, Malaysia (present study)	935	2.35:1		30.4	25.6	Male – perianal; Female - Posterior fourchette	Cryotherapy, podophyllin, tri-chloroacetic acid, imiquimod
		656	279				
Nyári et al.[14], 2004, Hungary	397	0	397	35.5	N/A	N/A	N/A
Dinh et al.[15], 2007, USA	11 454	1:1.12		35- 44	N/A	N/A	N/A
Kjaer SK et al.[16], 2007, Nordic countries	7351	0	7351	31.8	N/A	N/A	Suggest prophylactic HPV vaccine
Nyitray et al.[17], 2008, USA	222	222	0	18 –29	0	N/A	N/A
Suligoi et al.[18], 2008, Italy	63	0	63	25–34	0	N/A	Advice vaccination
Castellsague et al.[19], 2009, Spain	56 446	1.29:1		31	N/A	N/A	Imiquimod or podophyllotoxin
Marra et al.[20], 2009, Canada	39 493	N/A	N/A	20-29	N/A	N/A	N/A
Lin et al.[21], 2010, Hong Kong	721	4.55:1		18-30	N/A	N/A	N/A
Lee et al.[22], 2010, South Korea	167 767	1:2.33		30–34	N/A	N/A	N/A
Jiamton et al[13], 2014, Thailand	181	181	0	31.1	15	Penile shaft	Suggest quadrivalent HPV vaccine
Sonnenberg P et al[12], 2018, UK	9 902	1:1.45		20-25	N/A	N/A	Advice vaccination

N/A – Not available; HIV - human immunodeficiency virus; HPV – human papilloma virus; N/A – data not available

history of ever having used cocaine or street drugs, history of sexually transmitted infections, smoking, or immunosuppression.[15,24] This was similarly reflected in our observation as more than half of our cohort had more than one sexual partner while 17.6% had other concomitant sexually transmitted infections.

Limited data is available on the prevalence of AGWs in pregnant women. Our cohort showed that a quarter of the female patients with AGWs were pregnant. AGWs in pregnancy has an implication on the mode of treatment and delivery. Caesarean delivery is indicated for women with genital warts if the pelvic outlet is obstructed or if vaginal delivery would result in excessive bleeding.[1] Rarely, HPV types 6 and 11 can cause respiratory papillomatosis in infants and children.[24,25] Whether caesarean section prevents respiratory papillomatosis in

infants and children is however, unclear.[25]

Treatment options for AGWs include patient-applied (podofilox, imiquimod), physician applied (podophyllin, trichloroacetic acid, interferon) and ablative treatments (cryotherapy, surgical removal, laser treatment).[24] We provide all modalities of treatment for AGWs at our centre except podofilox, interferon and laser treatment. If we exclude those who were referred for surgical excision of the lesions, an average duration of 2.16 months is required to remove the visible lesions in nearly 80% of our patients the treatment modalities provided. A study done in Canada also reported an average episode of care for genital warts of about 2 to 3 months.[20]

HPV type 16, 18 31 33 and 35 are occasionally found in anogenital warts (usually as coinfection with HPV 6 or 11). It is associated with foci of high grade squamous intraepithelial lesions particularly in persons who have HIV infections.[1] Squamous cell carcinomas arising in or resembling genital warts might occur more frequently among immunosuppressed persons. While AGWs are diagnosed based on clinical appearance, a biopsy to assess lesions suspicious of malignant transformation may be indicated. Screening for anal intraepithelial neoplasia by cytology can be considered in view of the increased incidence of anal cancer in HIV infected MSM.[27] A study demonstrated that biopsies of genital lesions consistent with condylomata acuminata from immunosuppressed patients contained significantly more HPV types than lesions from the control group.[28] HPV types associated with an increased risk of dysplasia (high-risk types) were in 100% specimens from immunosuppressed patients in which 24 patients were immunosuppressed, with a third were organ transplant recipients and the remaining were infected with HIV.[28]

Genital warts in HIV infected patients are more difficult to treat with frequent recurrences.[29] Our HIV infected patients required higher number and longer treatment duration in order to achieve about 70% clinical improvement. Interestingly the recurrence rate among our HIV cohort did not differ from those without HIV infection. The high recurrence rate described in the literature may be due to defects in cell-mediated immunity and untreated asymptomatic subclinical infections that may act as an unnoticed source of infection.[13]

AGWs can be prevented by the administration of the human papilloma virus vaccine. Three prophylactic vaccines, Cervarix®, Gardasil® (quadrivalent HPV) and Gardasil®9 (nano valent HPV), have been approved by the Food and Drug Administration (FDA) in the United States to protect against HPV infections.[30] Gardasil® vaccine protects against HPV 6 and 11, which are associated with 90% of genital warts and 95% of recurrent respiratory papillomatosis.[31] In clinical trials conducted with 92 to 319 HIV patients, seroconversion to HPV was observed in 75-100% of vaccinated HIV patients.[32-34] Gardasil®9 is also expected to protect against ~80-85% cases of HPV-associated vaginal cancers, 90-95% of HPV-associated anal cancers, 85-90% of HPV-associated vulvar cancers.[35]

Gardasil® has been the vaccine of choice worldwide. It has been chosen by health authorities in the United States, Australia, New Zealand, Canada, Switzerland, Italy, Spain, and Sweden for regional or national vaccination programmes against cervical cancer.[36] The United Kingdom substituted the bivalent vaccine with the quadrivalent one in 2012, since the government clarified that the aim is to protect girls against the types of HPV that cause cervical cancer and those that cause genital warts.[37] In Spain, there was a decline in genital warts when female subjects were vaccinated with quadrivalent HPV vaccine.[38] In Australia & New-Zealand, cases of genital warts reduced after the introduction of HPV vaccine.[26,39]

In Malaysia, the routine vaccination was started in 2010 for all teenage girls. The only vaccine proposed by the ministry to be used in hospitals and clinics of ministry of health is bivalent type (Cervarix®) from GlaxoSmithKline (GSK)

Biological manufacturer to prevent a cervical cancer caused by HPV type 16 and type 18.[40] However, evidence has shown that bivalent vaccine does not confer cross-protection against genital warts caused by HPV 6 and 11, therefore teenage girls who have been vaccinated with Cervarix® can still contract genital warts.[12] Based on this knowledge, it would be best that quadrivalent vaccine (Gardasil) or Gardasil 9 be administered instead. Gardasil® should also be offered to MSM (up to and including 45 years of age) as studies have shown that MSM have a higher incidence of HPV infection and related diseases.[37, 41] This knowledge, along with the expectation that MSM will benefit less from herd protection from the vaccination of women, quadrivalent vaccination should be offered to MSM attending sexual health and HIV clinics, as a cost-effective intervention.[12,42]

The biggest challenge we face in our setting is to ensure patients stay in contact with our tertiary medical services and adhere to the treatment plan. If the AGWs are inadequately managed, these patients will be a risk to others. There are several factors contributing to the high rate of lost to follow up in our cohort. Patients tend to miss their appointments once they experience resolution of symptoms. Other reasons included the inability to adhere to frequent follow-up as patients are normally seen every two weeks in the GUM clinic until complete resolution of visible warts. Effective lost to follow up strategies need to be endorsed and enforced to overcome this issue as described by Rayment et al.[43] Primary care physicians and other health care provider such as home visit health care team may need to be involved in this initiative. Further studies are needed to determine the causes of the high lost to follow up rate. Strategies that can be implemented to reduce this high rate include structured patient education on first consultation and a more flexible appointment system etc.

Conclusion

AGWs was more commonly observed in male. The most frequent site of involvement was perianal for male (52.6%) and posterior fourchette in female (45.2%). The most frequent treatment modality used was cryotherapy (86.4%) and about 41.5% required combination of treatments. About 6.2% experienced recurrence. The human papilloma virus vaccination in our national immunization should be promoted to male students to reduce the prevalence of genital warts.

Conflict of Interest Declaration

All authors have no financial/conflict of interest to disclose.

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