A Case of Penile Squamous Cell Carcinoma Associated with HPV58 Infection

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ABSTRACT We report the case of a 55-year-old man with penile squamous cell carcinoma (SCC). We found a mass in the patient's penis, which gradually increased in size. We performed a partial penectomy to remove the mass. Histopathology revealed a highly differentiated squamous cell carcinoma. Human papillomavirus (HPV) DNA was detected by polymerase chain reaction. HPV was found to be present in the squamous cell carcinoma, and sequencing analysis showed that it was type 58.

KEY WORDS: penile squamous cell carcinoma, HPV58, HPV vaccine

INTRODUCTION

Penis cancer was historically considered a rare type of malignant tumor that is associated with significant disability. However, recent research indicates that the incidence of penile cancer has increased in all countries (1,2). In South America and parts of Asia, the incidence of penile cancer can account for as much as 10% of adult male cancers (3). Squamous cell carcinoma is the most common type of penile cancer, accounting for more than 95% of all malignant penile cancers (4). Its etiology includes phimosis, HPV infection, smoking, and chronic inflammation (5). In 2016, the WHO made a major new adjustment to the classification of this tumor, differentiating it into two categories based on its association with human papillomavirus (HPV): non-HPV-associated squamous cell carcinoma of the penis and HPV-associated squamous cell carcinoma of the penis (6). HPV-related penile squamous cell cancers account for about half of the total. Among them, HPV16 is the most common virus strain in penile squamous cell carcinoma, followed by HPV6 and HPV18 (7). Herein we report a rare case of penile squamous cell carcinoma related to HPV-58 infection.

CASE REPORT

The patient was a 55-year-old man with a penile mass initially identified more than 2 years ago. The patient had an ill-defined soft elastic nodule of approx. 20×15 mm on the penis (Figure 1). The patient accidentally discovered a penile mass of the size of a grain of rice two years ago and was not concerned at that time. For 2 years, the mass gradually increased in size, and purulent secretions were visible at times. There was no inguinal involvement of the enlarged lymph nodes.

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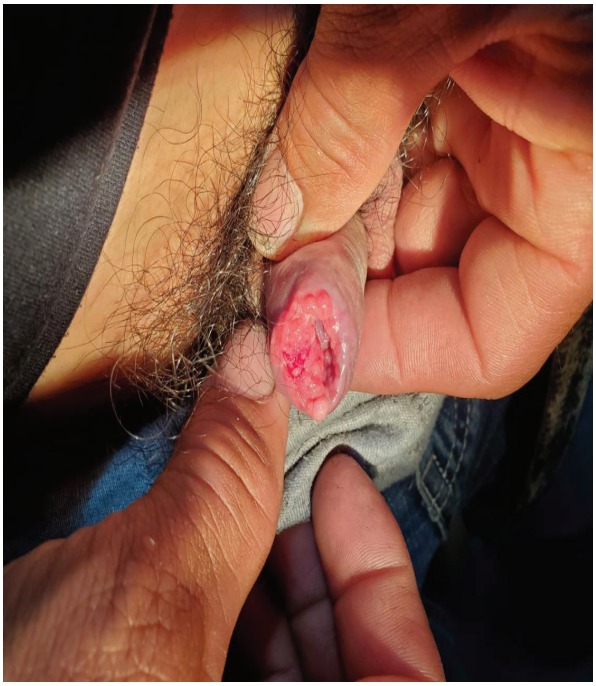

Figure 1. An ill-defined, soft elastic nodule on the penis with an approx. size of 20×15 mm.

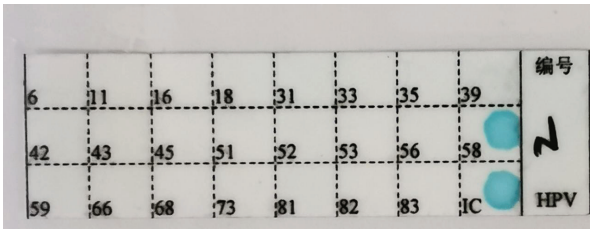

Figure 2. HPV DNA in the tumor was detected by polymerase chain reaction. HPV58 was detected.

The patient was in good health, not addicted to alcohol, had smoked for more than 10 years, and had quit smoking 1 year ago. The patient had a history of poor personal hygiene, with smegma often accumulating inside the foreskin. The patient denied having visited sex workers, and there was no history of similar disease in the family. The mass remained after anti-infection treatment at a local hospital, and he was referred to the outpatient department of dermatology and venereal diseases of our hospital. A biopsy specimen was removed from the lesion on the penis under local anesthesia. Pathohistological analysis of the biopsy indicated epidermal papillary hyperplasia with severe dysplasia, abundant infiltration of chronic inflammatory cells in the dermis consistent with Bowen

Table 1. Summary of HPV DNA Positivity in the Study Samples

	HPV type				
		Frequency	Percentage	Effective percentage	Cumulative incidence
effective	hpv 11	19	3.6	3.6	3.6
	hpv 18	24	4.6	4.6	8.2
	hpv 26	1	.2	.2	8.4
	hpv 28	2	.4	.4	8.7
	hpv 31	4	.8	.8	9.5
	hpv 33	13	2.5	2.5	12.0
	hpv 35	5	1.0	1.0	12.9
	hpv 39	3	.6	.6	13.5
	hpv 42	1	.2	.2	13.7
	hpv 45	10	1.9	1.9	15.6
	hpv 51	1	.2	.2	15.8
	hpv 52	4	.8	.8	16.5
	hpv 53	2	.4	.4	16.9
	hpv 56	4	.8	.8	17.7
	hpv 58	3	.6	.6	18.3
	hpv 59	3	.6	.6	18.8
	hpv 6	16	3.0	3.0	21.9
	hpv 66	2	.4	.4	22.2
	hpv 67	2	.4	.4	22.6
	hpv 71	1	.2	.2	22.8
	hpv 8	11	2.1	2.1	24.9
	hpv16	395	75.1	75.1	100.0
	total	526	100.0	100.0	

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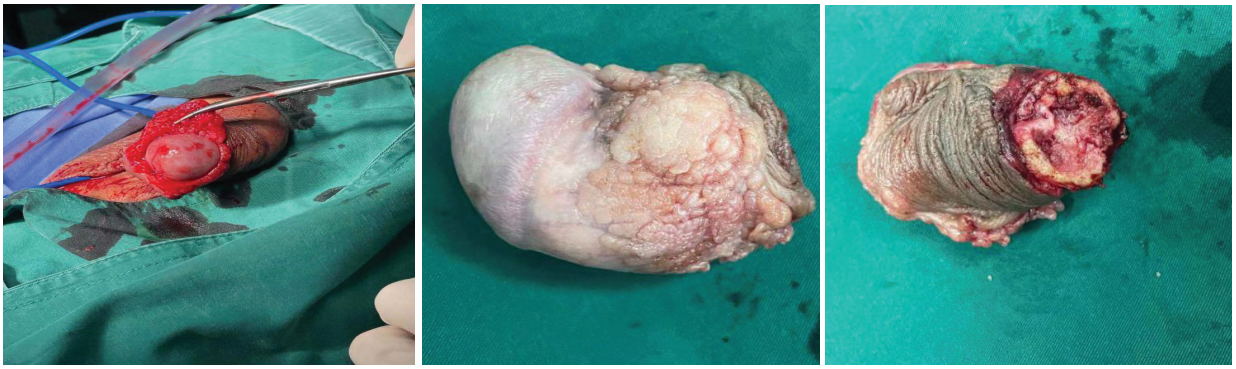

Figure 3. The affected part of the penis as seen intraoperatively and after excision.

Disease, and unclear lateral margin. The HPV typing of the lesion was conducted by polymerase chain reaction (PCR), and was positive for HPV58 (Figure 2). Blood was negative for HIV, TPPA, and RPR.

Considering the accuracy of the sampling site, the patient was referred to the urology department for further diagnosis and treatment. At the urology department, penile squamous cell carcinoma was diagnosed and partial penectomy was performed (Figure 3). According to histopathology, the excised material was consistent with highly differentiated squamous cell carcinoma of the coronal sulcus of the penis. Some of the tumor cells on the surface showed wart-like changes, some showed papillary growth, and some resembled carcinoma *in situ*. The lamina propria was involved, but there was no involvement of the urethral cavernosum, tunica albuginea and cavernosum of the penis, no lymphatic vessel infiltration was found, and no tumor was observed at the incision margin (Figure 4). Immunohistochemistry was P16 diffuse + (Figure 5), P40 positive, P53 scattered in a small amount of positive, CK5/6 positive, and Ki-67 index 90%. According to the AJCC Penile Cancer guidelines, the TNM grade was T1acN0M0. Patients with a low risk of PT1a tumor metastasis may choose regular monitoring without lymph node dissection. Therefore, we did not treat the lymph nodes but only removed the local lesions. Postoperatively, the patient was in generally good condition, with an unobstructed urinary duct, normal urine volume, and color. No recurrence was observed by the time of writing (six months post-surgery). But recurrence of regional lymph nodes generally occurs two years before follow-up and can last for up to five years. This patient had no enlarged lymph nodes during regular monitoring, but further subsequent monitoring was still needed.

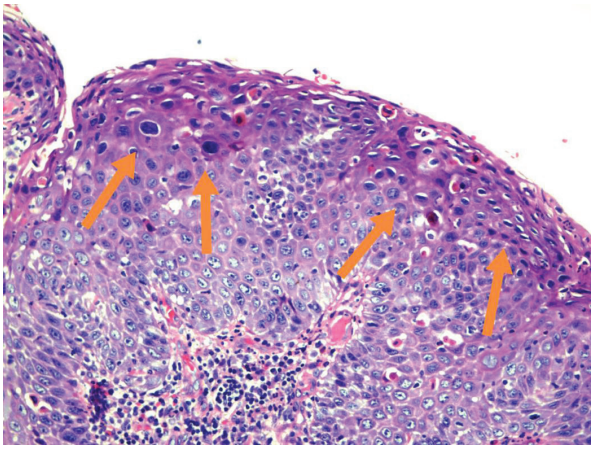

Figure 4. Pathohistologically, the tumor presented as highly differentiated squamous cell carcinoma of the coronal sulcus of the penis. Some of the tumor cells on the surface had a wart-like appearance. There was papillary growth, partly carcinoma in situ, involving the lamina propria.

DISCUSSION

Although the exact mechanism is unclear, studies have indicated that human papillomavirus (HPV) infection is related to the oncogenic impact of penile carcinoma (8). In reviewing the literature, we found that P16INK4A is overexpressed in tumors associated with HPV infection (9) and is a surrogate marker for HPV-induced transformation with a high probability of malignancy (10). Compared with CISH, P16INK4A appears to be a better predictor for HPV-associated penile squamous cell carcinoma, with a sensitivity and negative predictive value of 72 and 62%, respectively (11). Therefore, we conducted an immunohistochemical analysis in our case, and the results showed diffuse positivity for P16, while pathohistological examination found that some of the tumor cells showed condyloma like changes with morphological characteristics of HPV virus infection, all of which suggested that HPV played a role in the malignant transformation in this case.

We can therefore confirm that this case of penile carcinoma was associated with HPV58 infection. We reviewed 14 studies on SCC in the recent decade.

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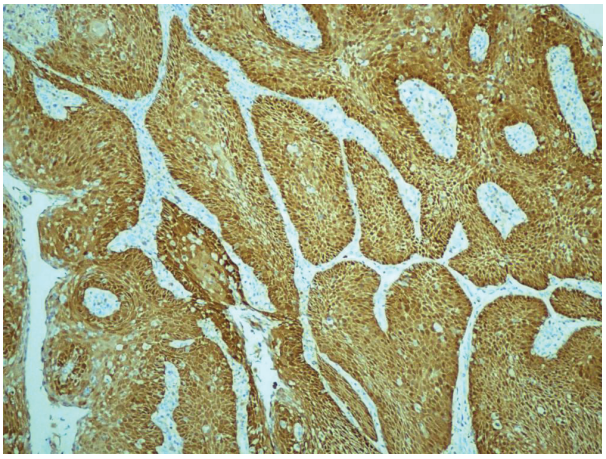

Figure 5. Immunohistochemistry showing overexpression of P16INK4A (magnification ×100). The cytoplasmic staining was strong and diffuse, suggesting a high likelihood of HPV infection.

A statistical analysis of the SCC cases illustrates the available data (12-25). These statistics selected only cases of single type HPV. A total of 22 HPV types were detected in 526 cases with HPV-positive penile cancer (Table 1). The most common types were HPV16 (75.1%), HPV18 (4.6%), and HPV11 (3.6%), while HPV58 was detected in only 3 cases (0.6 %) (Figure 6). No cases of squamous penis cancer caused by HPV58 have been reported. Thus, penile cancer caused by HPV58 infection is extremely rare. Furthermore, studies have explicitly proposed the prognostic value of HPV type 58 in penile cancer, but there is literature indicating that HPV-positive penile tumors tend to have a better prognosis compared with HPV-negative tumors (26). Moreover, HPV type 58 is classified as a high-risk HPV type, and the presence of high-risk human papillomavirus-DNA in penile cancer often has a survival advantage (27,28). In our case, our patient had no abnormal changes during the years of postoperative follow-up and had no enlarged inguinal lymph nodes on ultrasound, with a good prognosis and no recurrence. However, the patient is still in follow-up.

It should be noted that this patient also had a history of foreskin elongation, which may have also played a role in the pathogenesis of penile squamous cell carcinoma. A systematic analysis of 24,401 men in 2017 found a significant reduction in HPV prevalence in circumcised men compared with uncircumcised men (odds ratio (OR): 0.68; 95%CI: 0.56-0.82) (29). Furthermore, men who do not consistently use condoms have a higher incidence of HPV infection (30). This suggests that there are multiple factors predisposing men to HPV infection. Therefore, we believe that circumcision and safe sex can help prevent HPV infection.

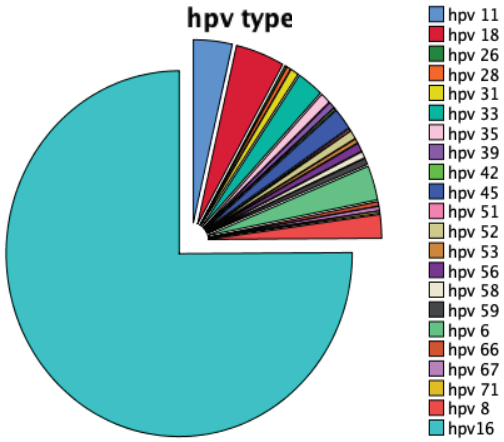

Figure. 6. Distribution of HPV types in penile cancerous lesions.

A large international study recently assessed HPV infection rates in tissue samples from penile malignancies over a decade. The study analyzed 1,664 cases of penile cancer, and HPV DNA was found in 51.0% of the samples (31). This was higher than the 33.1% infection rate reported by Alemany *et al*. in 2016 (32), further indicating that there is an increasing need to prevent HPV infection.

Since a large proportion of penile cancers are associated with HPV infection, this also highlights the potential benefits of HPV vaccination in the prevention of penile cancer. In a study of men of all ages, healthy foreskin samples were examined for the rate of high-risk HPV infection. The results showed that high-risk HPV subtypes were found in 60.6% of adolescents (11-20 years old) and 58.3% of adults (>20 years old). The prevalence (59.8%) was mainly concentrated in the age group with an estimated high rate of sexual activity (>14 years old) (33). These data suggest that high-risk HPV infections are common among young men. The ACIP therefore recommended routine HPV vaccination for young men in 2011 after reviewing data on efficacy, vaccine safety, burden of disease, cost-effectiveness, and programmatic considerations (34). In 2014, the FDA approved vaccination for the prevention of HPV6, 11, 16, 18, 31, 33, 45, 52, and 58 subtypes (35), which account for around 90.5 percent of HPV DNA-positive penile cancers (36). Vaccination programs for adolescents of both sexes have been implemented in many countries, including Australia, Brazil, Canada, Croatia, United Kingdom, Germany, Israel, Italy, New Zealand, Sweden, and United States (37). Some countries, such as the UK, also offer free HPV vaccination to homosexuals (38). A population-based model for the transmission of a single type of HPV and data from Sweden suggest that combined male and female vaccination leads to an approximately 17% reduction in HPV prevalence compared

with female-only vaccination (39). In countries with vaccination programs for both sexes, research should continue to assess the impact of HPV vaccination on HPV-related cancers other than cervical cancer, particularly among men. Although the current HPV vaccine is prophylactic and does not treat pre-existing HPV infections or related diseases (40), researchers are investigating therapeutic vaccines that elicit cellular immune responses to treat identified infections and malignancies (41). For example, combination therapies with antibodies against programmed death 1 ligand (PD-L1) and therapeutic HPV vaccines have been reported to inhibit tumor growth and increase cellular immune responses (42). Because there is currently no treatment for HPV infection, prevention methods and increased patient education are particularly important.

CONCLUSIONS

HPV58 infection in male patients has not been taken seriously in the past because it is usually asymptomatic. In the future, the prevalence of HPV 58 in penile squamous cell carcinoma may increase with the spread of viral subtypes, which requires our close attention. We urge patients to attend checkups regularly, especially those with excessive foreskin length, and to receive appropriate treatment when necessary so as to avoid unfavorable results. A significant proportion of the global population will continue to be affected by HPV-related cancers and precancerous lesions. Although there has been some success with HPV vaccination in women to prevent cancers caused by HPV, clear results are still lacking for the male population. Further comprehensive studies are required to fully evaluate the benefits of widespread vaccination in the male population. It is hoped that the incidence of penile cancer will be further reduced in the future through a vaccination program aimed at men.

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