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*Case Report*

# Papillary urothelial carcinoma with squamous differentiation in association with human papilloma virus: case report and literature review

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**Abstract:** Background: The human papilloma virus (HPV) is a carcinogen known for its strong association with cervical cancers and cervical lesions. It is also known to be associated with a variety of squamous cell carcinomas in other areas, such as the penis, vulva, anus and head and neck. However, the association with urothelial carcinoma remains controversial. Here, we report a case of urothelial carcinoma with squamous differentiation associated with HPV-6/HPV-11. Case presentation: This is a case of a 70 year old man who presented with nocturia and pressure during urination. During the TURP procedure for what was clinically thought to be benign prostate hyperplasia with pathologic diagnosis as prostate carcinoma, a 2 cm papillary mass was found in the distal penile urethra. The papillary mass was found to be a high grade urothelial carcinoma positive for GATA 3 expression, with focal areas of squamous differentiation. The areas with squamous differentiation demonstrated koilocytic differentiation, which were positive for strong p16 expression. The tumor was found to harbor low risk HPV 6/11 by in situ hybridization. Conclusions: This study case demonstrates HPV infection with a low risk subtype (HPV 6/11) associated with an urothelial carcinoma with squamous differentiation and condylomatous features.

**Keywords:** Bladder cancer, condyloma, human papilloma virus, urothelial carcinoma

## Introduction

The human papillomavirus (HPV) is a well-known viral carcinogen with high-risk types (16, 18, 31, 33, etc.) associated with more than 90% of cervical cancers [1]. The viral oncogenes, E6 and E7, have been shown to inactivate tumor suppressor p53 and retinoblastoma proteins and initiate carcinogenesis. HPV has also been well-established to be associated with squamous cell carcinomas in other sites such as the penis, anus, vulva and head and neck [2-5].

The possible association of HPV and bladder cancer has been explored previously; however, its role is controversial. Some researchers have reported significant association of high risk HPV subtype infection and bladder carcinogenesis [6-8], while other papers have concluded that there is no causation between HPV and urothelial carcinoma [9, 10]. Molecular characterization of urothelial carcinomas showed that in at least 1 case, there was integration of HPV 16 into the tumor cells. While not conclusive, this indicates that viral infection may have a role in the development of a small percentage of urothelial carcinomas [11].

Squamous cell carcinomas of the bladder have low HPV frequency and is not likely to have a role in carcinogenesis as compared to cervical cancers [12]. However, urothelial carcinomas with condylomatous features have been reported to be HPV positive and commonly of the high-risk type [13, 14]. These are usually in a setting of immunosuppression or neurogenic bladder with prolonged catheterization [13]. Of

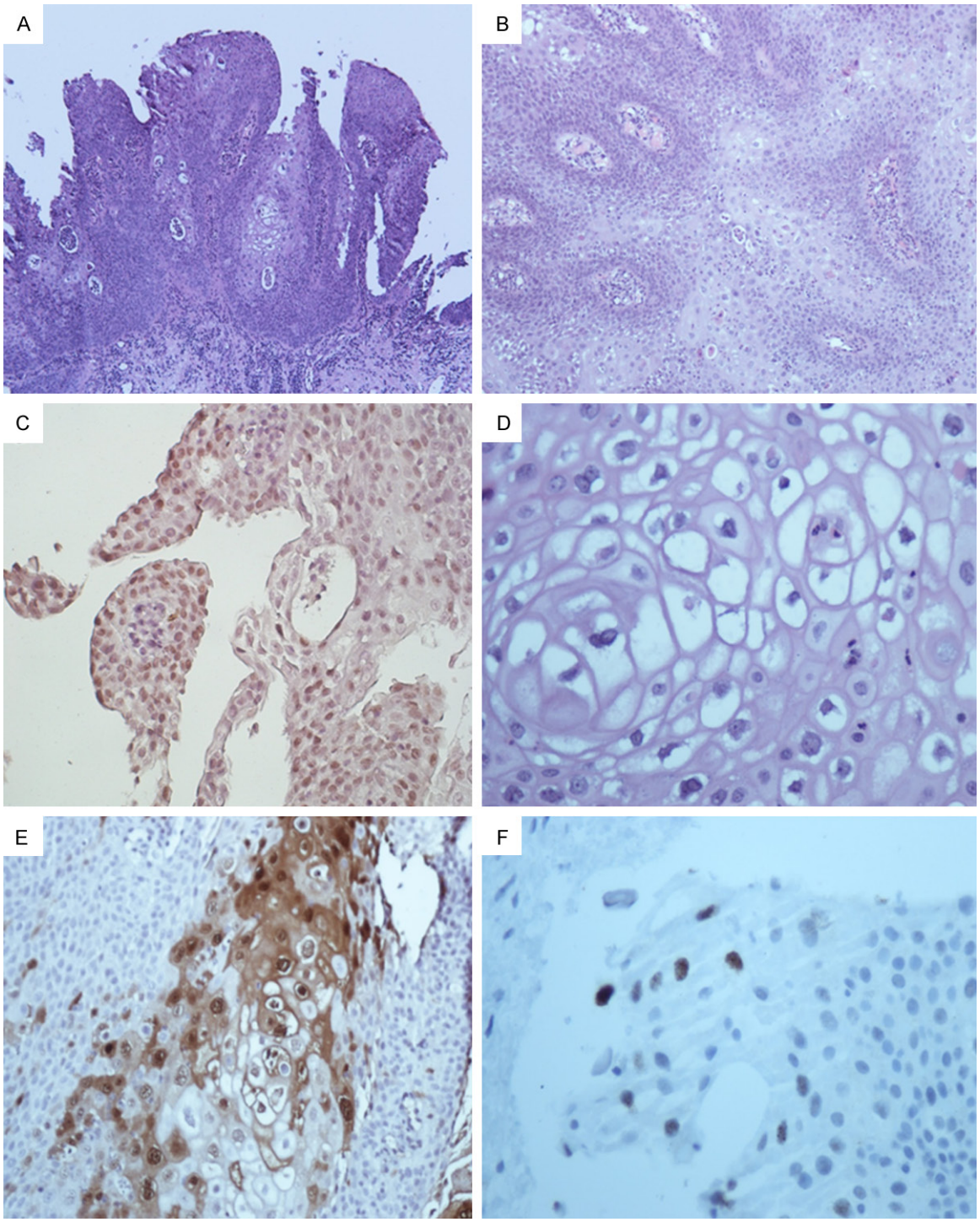


**Figure 1.** Sections of urothelial carcinoma demonstrate representative sections of urothelial carcinoma with squamous differentiation at 10X (A) and 20X (B). Urothelial carcinoma is stains positive for GATA-3 (C). Sections of urothelial carcinoma demonstrate HPV effect or koilocytic differentiation at 20X (D). Sections of urothelial carcinoma demonstrate positive p16 expression (E) and HPV6/11 expression (F).

note, both low-risk and high-risk HPV types have been detected in condylomas of the bladder [15, 16]. However, low-risk HPV types have been rarely, if never reported in urothelial carcinomas with squamous differentiation. Here we describe a case of low-risk HPV-positive papil-

lary urothelial carcinoma with prominent condylomatous features.

## Case presentation

This is the case of a 70 year old man who presents with nocturia and pressure during urination, with a history of gonorrhea as a young man and an unclear history of "polyps" in his urinary tract removed unspecified years ago. The patient also had a history of a small paratesticular mass that was thought to be a squealae of infection or trauma, for which he had been undergoing occasional scrotal ultrasound surveillance. He had a history of osteoarthritis, hyperlipidemia, peripheral neuropathy, chronic renal disease, chronic lower back pain, and periodic limb movements of sleep. Urological examination revealed calcified/sclerosed internal hemorrhoids overlying prostate. PSA was of 3.2. The patient was admitted for transurethral resection of the prostate (TURP) for what was clinically thought to be benign prostate hyperplasia.

During the TURP procedure, a 2 cm papillary lesion was seen in the distal penile urethra, near the fossa navicularis. This lesion was excised and sent for pathology with the prostate chips. A diagnosis of adenocarcinoma of the prostate with a Gleason score of 5 + 4 = 9/10 was made for the TURP specimen. The papillary lesion was diagnosed as high-grade urothelial carcinoma, with focal areas of squamous differentiation (**Figure 1A**, **1B**). Immunohistochemistry revealed positive expression of GATA-3, confirming the urothelial carcinoma diagnosis (**Figure 1C**). Focal areas of the squamous differentiation demonstrated koilocytic differentiation (**Figure 1D**). These areas were positive for p16 expression (**Figure 1E**).

Due to the presence of koilocytic differentiation and positive p16 expression, HPV infection was considered as a possibility. Immunohistochemistry was done to examine HPV protein expression. Three groups of HPV subtypes were tested. Immunohistochemistry showed positive expression for HPV 6/11 (**Figure 1F**), low risk subtypes [17] and negative for HPV 16-18 and HPV 31-33, both high risk subtypes [18].

## Discussion

This is a case of a high-grade urothelial carcinoma found incidentally as a 2 cm papillary lesion during a routine transurethral resection of the prostate, at the distal penile urethra, near the fossa navicularis. The urothelial carcinoma, confirmed by positive GATA-3 expression, had focal areas of squamous differentiation, which demonstrated koilocytic differentiation. Koilocytosis in squamous epithelium is a pathognomonic feature of both low risk and high risk HPV infection [19]. P16 was highly expressed, which is associated with both HPV-associated squamous cell neoplasm of the cervix and more than one third of squamous cell carcinomas of the urinary bladder [20]. We discovered that it was positive for low-risk HPV 6/11.

HPV 6 and HPV 11 are mostly associated with benign lesions. Oral papillomas and condylomas are generally caused by HPV 6 or HPV 11, while oropharyngeal squamous carcinomas and premalignant lesions are caused by HPV 16 and HPV 18 [21]. This holds true for cervical lesions, as HPV 16 and 18 infections account for almost 50% of all cervical cancers, while HPV 6 and 11 cause benign genital lesions [22]. High HPV infection rates have been reported in urothelial carcinomas. However, high risk HPV subtypes were reported as the main culprits [23], with HPV 16 genomic integration found in at least one case [11]. High risk HPV subtypes have been proposed as causative agents for low grade urothelial carcinomas in younger patients [12]. However, both low risk and high risk subtypes have been detected in condylomas of the bladder [15, 16].

This paper reports a case of high-grade urothelial carcinoma, with squamous differentiation, associated with infection of a low risk HPV subtype. HPV 6 and 11 are normally not known to cause malignancy. However, certain cases of recurrent respiratory papillomatosis, a disease caused by HPV 6 and HPV 11, have been reported to progress to squamous metaplasia with dysplasia and squamous carcinoma of the esophagus [24, 25]. This case report exudes an association between HPV infection and urothelial carcinoma with squamous metaplasia. Its role in tumorigenesis is unclear.

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## Disclosure of conflict of interest

None.

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