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Primary Urethral Carcinoma: A Case Report and Review of the Literature

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Abstract

Primary urethral carcinoma is a kind of rare clinical disease, especially urethral multiple lesions *in situ*, and there has been far less emphasis on understanding the diagnosis and treatment for it. Here we reported a rare case of primary urethral carcinoma. The patient came to the urology clinic due to difficulty of urination for 3 months, aggravated with gross hematuria for 1 day. Cystoscopy founds multiple cauliflower-like neoplasm originating in the prostatic urethral, bulbous urethral and penile urethral. Moreover, there are condyloma acuminate and occasional urinary tract irritation medical history with the patient. Preoperative biopsy or postoperative pathology revealed high-grade urothelial carcinoma. The surgeon took tumor resection of urethra for the patient. And then the immunohistochemical analysis of the specimen was carried out and results confirmed the diagnosis. After the operation, 6 cycles of pirarubicin were implemented and there is no evidence show harmful reaction. During a 6-month follow-up, we find no evidence for tumor recurrence, metastasis or surgical complications. After all, primary urethral urothelium carcinoma is rare in clinical practice with particular clinical and pathological characteristics. There is still no mature treatment plan and should be studied further.

Keywords: Primary urethral carcinoma; Urothelial carcinoma; Diagnosis; Treatment

Abbreviations

SEER: Surveillance, Epidemiology and End Result; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; H&E: Hematoxylin-Eosin

Background

Primary urethral carcinoma is a rare cancer, accounting for <1% of all malignancies [1]. According to related reports of epidemiological investigation. In 2013, the prevalence of urethral carcinoma in the 28 European Union countries was 3986 cases, with an estimated annual incidence of 1,504 new cases and a male/female prevalence of 2.9:1 [2]. In the United States, a database analysis from the Surveillance, Epidemiology and End Results (SEER) showed that the incidence of primary urethral carcinoma peaked in the >75-yr age group (7.6/million), with an age standardized rate of 4.3/million in men and 1.5/million in women, compared with almost negligible in those aged <55-yr (0.2/million) [3]. There is lack of data of prevalence of urethral carcinoma from Asia region. But we speculate that prevalence of urethral carcinoma is different in races and regions. The predominant histological type of urethra is urothelium carcinoma (54% to 65%), followed by squamous cell carcinoma (16% to 22%), and adenocarcinoma (10% to 16%) [2,4]. Urethral carcinoma usually occurs in the urothelium of the prostatic urethra, squamous cell carcinoma commonly takes place in the distal urethra. Primary urethral carcinoma of multiple sites of the urethra, where typically is lined by urothelium cell, is particularly rare. From the perspective of etiology, there are various predisposing factors have been reported, such as urethral strictures [5,6], chronic irritation after intermittent catheterization/urethroplasty [7-9], external beam irradiation therapy [10], radioactive seed implantation [11], chronic urethral inflammation or urethritis following sexually transmitted diseases (i.e. condyloma acuminate associated with human papilloma virus 16) [12,13], lichen sclerosis [11], urethral diverticula [14-16] and recurrent urinary tract infections [17]. The specific pathogenic mechanism remains to be studied. Due to the rarity of this disease, the etiology of primary urethral carcinoma is not studied deeply and there is still no recognized treatment plan. In the present study, we carefully summarized some of the recent literature concerning the primary urethral carcinoma and analyzed the clinical, histological and immunohistochemical features. We

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Table 1: Previous case reports on the primary urethral carcinoma in recent years.

Author year	Gender	locations	Symptoms	Therapies	Follow up	Outcomes
Zhou et al. [2019]	male	prostatic	lower urinary tract obstructive	radical cystoprostatectomy; bladder irrigation with cisplatin and gemcitabine	6 months	no recurrence and metastasis
Wang et al. [2020]	male	penile	urinary stream bifurcation and dysuria	partial urethrectomy; bladder irrigation with epirubicin	61 months	no recurrence and metastasis
Pratama et al. [2021]	female	anterior	urinary retention Burning sensation	Urethrocysto-uretherectomy (anterior exenteration) later	-	-
Chen et al. [2019]	female	anterior	difficulty in urinating, lower abdominal pain during urination	primary tumor resection; bladder perfusion chemotherapy	1 year	lung metastasis
Jakub Krukowski et al. [2018]	male	Bulbous membranous; lymphatic metastasis	urethral stricture	suprapubic cystostomy	-	-
Guo et al. [2022]	male	prostatic, bulbous penile	urination difficulty; gross hematuria	tumor resection of urethra; bladder irrigation with epirubicin	6 months	no recurrence and metastasis

concluded current available evidence for the diagnosis and treatment for this rare aggressive neoplasm (Table 1).

Case Presentation

A 60-year-old man had difficulty of urination for 3 months, aggravated with gross hematuria for 1 day, and then he came to the urology clinic. Apart from the prostatic hyperplasia that was treated with surgical operation 3 years previously, there is no other accompanying disease was present. During the consulting, the patient reported that he took an operation owing to condyloma acuminate and occasional urinary tract irritation. There are no abnormalities after physical examination. F-PSA, T-PSA and FPSA/TPSA maintained within normal range. Computed Tomography (CT) scan of the abdomen and pelvis revealed small kidney stones. No pelvic lymphadenopathy was reported. Subsequently, he underwent cystoscopy and biopsy. The surgeon found multiple cauliflower-like neoplasms in bulbar urethra, prostate urethra and penile urethra are involved with nothing abnormal in bladder (Figure 1). After that, the surgeon took tumor resection of urethra for the patient. Because it's hard to cut neoplasm down from urethra, they took external urethrotomy first. The patient subsequently underwent bladder perfusion on the day after surgery. The patient didn't have any complications during a week after the successful operation. The results of the Postoperative pathology showed primary urethral carcinoma. Histopathological examination showed high-grade urothelial carcinoma, meanwhile, Immunohistochemical analysis was implemented and reported as following: CK7(+), P63(+), Uroplakin III(+), PSA(-), CD56(-), as same as the diagnosis of high-grade urothelium carcinoma (Figure 2). Furthermore, after surgery, the patient received 6 cycles of pirarubicin treatment without any harmful reactions. Imaging examination found no tumor recurrence during half a year follow-up period.

Discussion and Conclusion

As a kind of rare cancer, it has been about 200 years since primary urethral carcinoma was described in human. According to relevant epidemiological data, crude incidence of primary urethral carcinoma in Europe is 0.12 per 100,000 people per year (transitional cell carcinoma of urethra 0.09, squamous cell carcinoma with variants of urethra 0.02, adenocarcinoma with variants of urethra 0.01) [18]. At the same time, incidence of primary urethral carcinoma in the US is 0.22 per 100,000 people per year (transitional cell carcinoma of urethra 0.15, squamous cell carcinoma with variants of urethra 0.05, adenocarcinoma with variants of urethra 0.02) [19]. There is also relevant data show that African Americans appear to have greater rates of squamous cell cancer and adenocarcinoma than whites, in both men and women. The rates were the same for transitional carcinoma in African-American and white men [20]. Maybe the incidence of primary urethral carcinoma is different in different region and race. However, to the best of our knowledge, the Incidence of urethral carcinoma is extremely rare worldwide. About 45% to 57% patients with primary urethral carcinoma present with advanced symptoms. At the patient's first visit, visible hematuria or bloody urethral discharge is reported in up to 62% of the cases. Late symptoms include an extra-urethral mass (52%), bladder outlet obstruction (48%), pelvic pain (33%), urethral cutaneous fistula (10%), abscess formation (5%), or dyspareunia [21]. Although the cause is unknown, chronic inflammation plays a crucial part in the development of urethral cancer. According to relevant reports, chronic urethral inflammation /urethritis following sexually transmitted diseases (i.e., condyloma acuminatum associated with human papilloma virus 16) have correlations with the incidence of primary urethral carcinoma. The infection of human papilloma virus 16 is confirmed in this case. At present, there is still a lack of relevant mechanism research on how these factors lead to the formation of

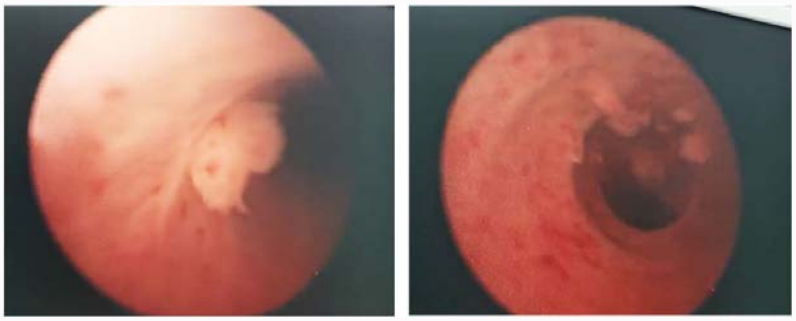

Figure 1: Urethroscopy image showing multiple cauliflower-like neoplasms in urethra.

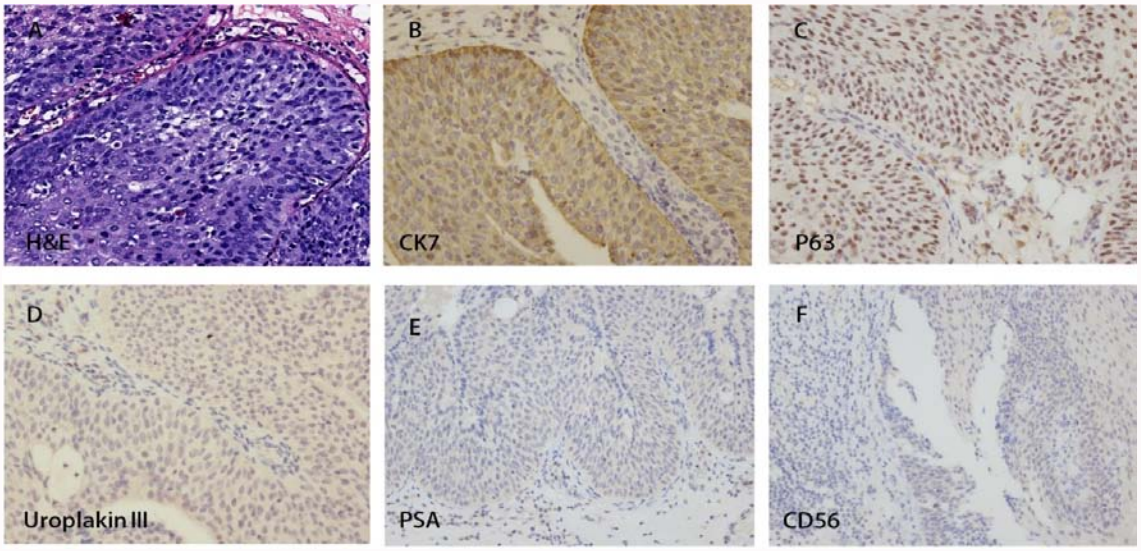

Figure 2: Microphotograph of the mass revealed high-grade urothelium carcinoma, hematoxylin-eosin, x40 magnification (A); Immunohistochemistry of the tumor tissue revealing: CK7(+)(B), P63(+)(C), Uroplakin III(+)(D), PSA(-)(E), CD56(-)(F).

Table 2: TNM classification (eighth edition) for urethral carcinoma [1].

T—primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Urethra (male and female)	
Ta	Noninvasive papillary, polypoid, or verrucous carcinoma
Tis	Carcinoma in situ
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades any of the following: corpus spongiosum, prostate, periurethral muscle
T3	Tumor invades any of the following: corpus cavernosum, beyond prostatic capsule, anterior vagina, bladder neck (extraprostatic extension)
T4	Tumor invades other adjacent organs (invasion of the bladder)
N—regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node
N2	Metastasis in multiple lymph nodes
M—distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
Histopathological grading of urothelial and nonurothelial primary urethral carcinoma [2]	
Urothelial urethral carcinoma	
PUNLMP	Papillary urothelial neoplasm of low malignant potential
Low grade	Well differentiated
High grade	Poorly differentiated

Abbreviation: TNM: Tumor, Node, Metastasis (classification); PUNLMP: Papillary Urothelial Neoplasm of Low Malignant Potential

primary urethral carcinoma. Clinicopathological staging and grading for primary urethral carcinoma insist on the classification given by the Union for International Cancer Control in 2017 and the World Health Organization in 2016 (Table 2). Urine cytology has limited sensitivity of 50% to 80%, which is for reference only in diagnosis of primary urethral carcinoma [22]. Cystoscopy enables primary assessment of a urethral tumor in terms of tumor extent, location, and underlying histology [23]. The primary goal of radiological imaging for urethral carcinoma is to assess local tumor extent and detect lymphatic and distant metastatic spread. The accuracy of CT for clinical tumor and that of nodal staging predicting final pathological staging were found to be 72.9% and 70.6%, respectively [24]. Magnetic Resonance Imaging (MRI) can be used to evaluate local tumor extent and presence of regional lymph node metastases, focusing in particular on inguinal and pelvic lymph nodes [25-27]. Currently, histology is still the gold standard of primary urethral carcinoma diagnosis.

Diagnostic urethroscopy, cystoscopy and biopsy, or Postoperative pathology can confirm the diagnosis in the case reported above, the histopathology examination showed primary urethral carcinoma with Urothelial differentiation, Hematoxylin-Eosin (H&E) staining showing oval and pleomorphic cells with increased nuclear to cytoplasmic ratio, irregular nuclear contours, hyperchromatic nuclei, and increased mitosis. A series of Immunohistochemical detection was performed to make a final diagnosis, results showed: CK7(+), P63(+), Uroplakin III(+), PSA(-), CD56(-), and had provided another objective evidence to make final diagnosis. The recognized strategy in the treatment of primary urethral carcinoma depends on gender, stage, and location of the tumor. In early-stage distal primary urethral carcinoma, the first aim is to achieve local control of the tumor. More and more scholars advocate applying organ-preserving approaches in men if oncological safe. In women, radiations have similar outcomes and are commonly used because surgical resection caused a high rate of urinary incontinence and sexual dysfunction [28]. However, proximal lesions are more likely to advance than distal lesions and multimodal therapy by using chemotherapy, radiation, and surgery is required with the goal of improving patient outcomes [29]. There is article advocating multidisciplinary therapy is the gold standard treatment of proximal primary urethral carcinoma [30]. In the context of no prospective multi-institutional studies in treatment of primary urethral carcinoma, multi-mode treatment strategy should be the first choice for primary urethral carcinoma. Primary urethral carcinoma has the features like low incidence, high aggressiveness and poor prognosis. Urethra cystoscopy and biopsy is the gold standard of diagnosis. The diagnose of primary urethral carcinoma should be depended upon the accurate clinicopathological staging. Because there is no support from evidence-based medicine, multimodal treatment should be considered. In summary, this case report supports further clinical development for the diagnosis and treatment of primary urethral carcinoma. Thus, the research has great clinical interest and brings new and important clinical reference in the field of urethral cancer management.

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