Case Report
Primary multiple clear cell variant urothelial carcinomas of urinary bladder: a rare case report

Yutao Zhang¹, Jun Huang², Hao Feng³, Yun Tang¹

Departments of ¹Pathology, ²Urology, ³Radiology, The First People’s Hospital of Zigong, Zigong, China

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Abstract: Clear cell variant urothelial carcinoma of urinary bladder was very rare. There were only 6 report articles included by Pubmed and total 8 cases had been described till now. All of the past reports described single tumor of urinary bladder, but multiple carcinomas had not been reported. Here we reported a 65-years-old Chinese man who complained of intermittent gross hematuria and odynuria for more than 2 months in January 2013. Only one cauliflower-like tumor was detected approximately in the left wall of the urinary bladder with cystoscopy and the biopsy specimen was diagnosed as “urothelial carcinoma, high grade”. However, three tumors were found in anterior wall (∗2) near neck of urinary bladder and posterior wall (∗1) of the urinary bladder during transurethral resection of the bladder tumor. Typical urothelial carcinoma with partial clear cell appearance made it difficult to make a precise pathological diagnosis and immunohistochemical stain helped to diagnose the case as clear cell variant urothelial carcinoma, but not metastasis of the renal cell carcinoma. Finally, computerized tomographic scanning confirmed that there was no primary tumor in the kidney. The clinical and pathological characteristic had not been identified for the limited reports. More work should be done to know this kind of tumor well for guiding clinical therapy.

Keywords: Clear cell variant urothelial carcinoma, urinary bladder

Introduction
Urothelial carcinoma of urinary bladder could present many variants, for example squamous and glandular differentiation, and those variants existed commonly with different proportion with typical urothelial carcinoma component. Urothelial carcinomas with notable abnormal differentiation always belonged to higher histological grade and stage. Clear cell variant urothelial carcinoma of urinary bladder was very rare comparing with other variants and clinical-pathological characteristic had not been identified with the limited reports.

Case report
A 65-years-old Chinese man who complained of intermittent gross hematuria and odynuria for more than 2 months in January 2013. Laboratory investigation revealed blood prostate specific antigen (PSA) level was 4.78 ng/ml. Both ultrasonography and computerized tomography (CT) scanning showed multiple neoplasms of the urinary bladder wall (Figures 1 and 2). Nevertheless, only one cauliflower-like tumor was approximately detected in the left wall of the urinary bladder with cystoscopy and the biopsy specimen was diagnosed as “urothelial carcinoma, high grade”. In fact, three tumors were found in anterior wall (∗2, about 2 cm in diameter respectively) near neck of urinary bladder and posterior wall (∗1, about 0.5 cm in diameter) of the urinary bladder during transurethral resection of the bladder tumor (TURBT). Typical poorly differentiated urothelial carcinoma with partial clear cell appearance which presented with glycogen-rich, clear cytoplasm and severe nuclear atypia in a nested growth pattern made it difficult to make a precise pathological diagnosis (Figure 3). Immunohistochemical stain showed the tumor cells were positive for cytokeratin 7 (CK7), cytokeratin20 (CK20), Uroplakin III (focal and weakly) and EMA, but negative for PSA, vimentin, CD10, RCC, p63 and 34βE12 (Figure 4). Considering both histological appearance and immunohistochemical stain result, this case was diagnosed as clear cell variant urothelial carcinoma,
Clear cell variant urothelial carcinomas of urinary bladder

but not metastasis of the renal cell carcinoma. Finally, post-operation CT scanning confirmed that there was no primary tumor in the kidney. Consecutive irrigation of bladder with pirarubi-

Table 1. Reports of clear cell variant urothelial carcinoma. Nine cases, including ours, have been published till now

<table>
<thead>
<tr>
<th>Report</th>
<th>Age</th>
<th>Gender</th>
<th>Initial symptoms</th>
<th>Gross findings</th>
<th>Therapy</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kotliar et al.</td>
<td>71</td>
<td>Male</td>
<td>Gross hematuria bladder tumor</td>
<td>Large nodule</td>
<td>RC with ileal conduit and adjuvant chemotherapy</td>
<td>Death after 20 months</td>
</tr>
<tr>
<td>Braslis et al.</td>
<td>58</td>
<td>Female</td>
<td>Dysuria</td>
<td>Urethral cyst</td>
<td>Pelvic exenteration</td>
<td>No available data</td>
</tr>
<tr>
<td>Yamashita et al.</td>
<td>70</td>
<td>Male</td>
<td>Frequency, urgency, anuria</td>
<td>Stenosis lesion of right upper tract</td>
<td>Right nephro-ureterectomy</td>
<td>Alive after 6 months</td>
</tr>
<tr>
<td>Isono et al.</td>
<td>69</td>
<td>Female</td>
<td>Gross hematuria</td>
<td>Large bladder mass</td>
<td>RC with ileal conduit</td>
<td>No recurrence after 7 months</td>
</tr>
<tr>
<td>Kramer et al.</td>
<td>65</td>
<td>Male</td>
<td>Progressive LUTS and pyelocaliectasis on both kidneys</td>
<td>Non-papillary pedunculated bladder tumor</td>
<td>TURBT</td>
<td>No recurrence after 20 months</td>
</tr>
<tr>
<td>Persec et al.</td>
<td>72</td>
<td>Male</td>
<td>Painless macroscopic hematuria</td>
<td>Non-papillary tumor mass on the vesical trigonum</td>
<td>RC with ileal conduit</td>
<td>Death after 14 weeks</td>
</tr>
<tr>
<td>Our case</td>
<td>65</td>
<td>Male</td>
<td>Intermittent gross hematuria and odynuria</td>
<td>Three cauliflower-like bladder tumors</td>
<td>TURBT and adjuvant chemotherapy</td>
<td>Recurrence after 3 months</td>
</tr>
</tbody>
</table>

RC, radical cystectomy; TURBT, transurethral resection of the bladder tumor; LUTS, lower urinary tract symptoms. *Some data of this table was cited from Kramer’s case report.

Figure 1. Computed tomography demonstrating multiple neoplasms of the urinary bladder wall (yellow arrow).

Figure 2. Computed tomography demonstrating multiple neoplasms of the urinary bladder wall (yellow arrow).

Figure 3. Hematoxylin and eosin (H&E) stained section showing diffuse glycogen-rich, clear cytoplasm and severe nuclear atypia in a nested growth pattern. Original magnification, ×400.

Figure 4. Higher power view of representative cytoplasmic immunostaining of CK7 in clear cell variant urothelial carcinoma. Original magnification, ×400.

cin (40 mg) was administered and general condition of the patient had kept well for 15 months.

**Discussion**

In 2004, several variants of urothelial carcinoma, common subtypes including squamous differentiation, glandular differentiation, nested variant and microcystic variant, had been described in the World Health Organization (WHO) histological classification of tumours of the urinary tract. Clear cell variant was a very rare subtype of urothelial carcinoma of urinary bladder. There were only 6 report articles included by Pubmed and total 8 cases had been described till now (Table 1) [1-6]. All of the past reports described single tumor of urinary bladder, but multiple carcinomas had never been reported. This was the ninth case report of clear cell variant urothelial carcinoma and the first case report of multiple carcinomas.

The clinical and pathological characteristic of clear cell variant urothelial carcinoma had not been approached. Based on the total 9 report ed cases, predilection of clear cell variant urothelial carcinoma was gerontal (58-72 years old, average 67.8 years old) and male patients (male:female = 6:3). Hematuria was the most common initial symptoms (6/9). Nevertheless, diverse gross finding would be presented during cystoscopy examination including large nodule, urethral cyst, stenosis lesion, papillary or non-papillary pedunculated bladder mass etc. Clear cell appearance could commonly be detected during microscopical observation. However, clear cell appearance could be seen in carcinoma arising in several sites, including prostate, breast, uterus, ovary and kidney [7, 8]. For this reason, it was difficult to make sure the primary site and the differential diagnosis was especially important when we meet such case. Firstly, clear cell adenocarcinoma was more frequent than clear cell variant urothelial carcinoma in urinary bladder. The histopathology of our case showed the tumor cells with glycogen-rich, clear cytoplasm and severe nuclear atypia in a nested growth pattern, but never finding typical glandular or tubule-cystic pattern and hobnail cells of adenocarcinoma. Furthermore, immunohistochemical positivity for CK7 deeply identified an urinary tract origin but not mullerian system. Second, immunohistochemical stain for RCC, CD10, vimentin and PSA were performed in order to make sure the primary site and the corresponding negative result ruled out metastasis of clear cell renal cell carcinoma and prostate adenocarcinoma. Lastly, clear cell carcinoma of breast and ovary need not be considered almost for male patient.

Although radical cystectomy or TURBt and adjuvant chemotherapy had been administered, but the patients could be alive for only 20 months at the most according to limited follow-up data [3, 6]. Those patients were susceptible to local recurrence and infiltration to adjacent organ [1]. For the present case, the MIB-1 positive index was 60-70% and it revealed a similar poor prognostic. However, the patient had kept well for 15 months.

In brief, clear cell variant was a rare subtype of urothelial carcinoma. Gerontal and male patients had the predilection to suffer from this tumor. Clear cell adenocarcinoma of urinary bladder should be considered in differential diagnosis and primary site diagnosis could only be made after immunohistochemical detection and radiological examination which could rule out metastasis of clear cell renal cell carcinoma and prostate adenocarcinoma. More clinical and pathological knowledge should be obtained to know biological behaviors of this tumor well. There was a long way for us to explore the better diagnostic and therapeutic options for this rare tumor.

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**Disclosure of conflict of interest**

None.

**Address correspondence to:** Dr. Yutao Zhang, Department of Pathology, The First People’s Hospital of Zigong, Zigong, Sichuan 643000, China. Tel: +86-0813-2112267; Fax: +86-0813-2104640; E-mail: bondyzyt1999@163.com

**References**


3387
Clear cell variant urothelial carcinomas of urinary bladder


