Clear-cell variant urothelial carcinoma of the bladder: a case report and review of the literature

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Abstract

Clear cell variants of transitional cell carcinomas (TCC) of the bladder are extremely rare tumors. Only 6 cases have been reported until now. We report of a 67 year old man who presented with fast growing tumor disease. While initial diagnosis showed localized bladder tumor, final histopathology revealed pT4, G3, L1 urothelial carcinoma with clear cell differentiation. No more than 14 weeks after initial diagnosis the patient died from multi-organ failure after unsuccessful salvage laparotomy which showed massive tumor burden within the pelvis and peritoneal carcinosis. This case demonstrated an extremely fast tumor growth. Therefore, patients with clear cell urothelial carcinoma should be treated vigorously and without time delay. We present a case of clear cell variant of TCC which exhibited an extremely aggressive behavior. To our knowledge this is the fifth report of this rare disease.

Introduction

Approximately 15% of carcinomas of the bladder account for variants other than the most common urothelial carcinoma. The four major categories are squamous cell carcinoma, adenocarcinoma, undifferentiated carcinoma and variants of urothelial carcinoma. Within the latter category, squamous, trophoblastic, glandular, micropapillary, nested and small cell differentiation are well described. However, little is known about urothelial carcinoma of the bladder with clear cell differentiation.

Case Report

A 65-year-old white male presented with progressive lower urinary tract symptoms and worsening of general condition. His past medical history was unremarkable. Laboratory investigation revealed elevated serum creatinine levels (139 μmol/L). Ultrasonography showed III pyocolicetasia on both kidneys, thickening of the urinary bladder wall as well as residual urine of approx. 500 mL. Blood prostate specific antigen (PSA) level: 2.5 μg/L. After insertion of an indwelling urinary catheter creatinine levels did not decrease and the pyocolicetasia remained. The patient underwent cystoscopy. Distal ureteral stenoses on both sides were recognized and ureteral stents were inserted. Non-papillary, solid tumor masses were found on the vesical trigonium and were removed by transurethral resection (TURBl). The pathohistological examination revealed poorly differentiated urothelial carcinoma of the clear cell variant with detrusor muscle infiltration (pT2a, G3). Computed tomography (CT) scan demonstrated 14 mm bladder wall thickening, no tumor invasion in perivesical tissue and no evidence of metastasis (Figure 1). Shortly after diagnosis, the patient was scheduled for radical cystectomy and ileal conduit. Final pathohistological examination confirmed the diagnosis of urothelial carcinoma clear cell variant, infiltrating the perivesical tissue, prostate and seminal vesicles (pT4, L1, G3, R1). Microscopic examination of the specimen exhibited diffuse glyocogen-rich, clear cytoplasm and severe nuclear atypia in an alveolar growth pattern (Figure 2). Glandular differentiation was not observed. Immunohistochemical staining showed positivity for cytokeratin 7 (CK 7), cytokeratin 20 (CK 20) and cytokeratin 8/18 (Table 1). The problematic feature of clear cell variant urothelial tumors of the urinary tract 2004, (WHO: histological classification of tumors of the urinary system and male genital organs). Clear cell variant of urothelial cancer is a very rare subtype of glandular neoplasms to which also adenocarcinoma must be mentioned. A limited number of cases have been reported up to date; this is the fifth report of this rare variant of transitional cell carcinomas (Table 1). The problematic feature of clear cell variant urothelial carcinoma can be approached from two directions: histopathologically and clinically. Clear cell carcinoma can arise in almost any site including prostate, kidneys, uterus, ovary, vagina, lung and breast. Therefore it might be difficult to diagnose the primary site. Based on the urinary tract, clear cell features within the bladder have been mostly associated with adenocarcinomas that have been reported to be more frequent than clear cell variant urothelial carcinomas. The histopathology in our patient revealed multiple layers and severe nuclear atypia in an alveolar growth pattern (Table 2, Figure 2). Typical pattern of adenocarcinomas of the bladder such as glandular differentiation, tubulocystic or papillary morphological patterns as well as hocknail cells were not observed. Although not being a clear feature for differentiation immunohistochemical positivity for CK7 might suggest an urothelial ori-
gin making adenocarcinoma less likely.1,10 To rule out metastasis, although CT-scans did not indicate primary sites other than the bladder, we performed immunohistochemical stains for PSA (prostate cancer), vimentin (kidney cancer), CA 15-3 (colorectal cancer), HMB-45/S-100/Melan-A (melanoma) and CD-10 (clear cell renal carcinoma).

The clinical course of clear cell variant urothelial carcinomas of the bladder is currently unknown due to the lack of larger case series. Only five cases with clinical information have been published (Table 1).2-5 Our patient showed aggressive behavior with rapid local recurrence and development of peritoneal carcinosis to which he succumbed only 14 weeks after initial diagnosis at which an advanced tumor stage had not been assumed. A similar clinical course has been described by Kotliar and colleagues.4 They reported of a 71-year old male who underwent radical cystoprostatectomy with ileal conduit due to muscle-invasive urothelial carcinoma clear-cell variant. Although computed tomography revealed no evidence of pelvic lymphadenopathy, nor metastatic disease, two pelvic lymph nodes were diagnosed carcinoma-positive. In spite of adjuvant chemotherapy the patient died after 20 months. In contrast a less aggressive course has been reported in two patients with urothelial clear cell carcinoma who were treated with TURBt, even though one patient had detrusor muscle invasion.5,5 Both patients

Table 1. Reports of clear cell variant transitional carcinoma. Seven cases, including ours, have been published until now.

| Report            | Age | Gender | Initial symptoms | Gross findings | Therapy                        | Follow-up          |
|-------------------|-----|--------|------------------|----------------|--------------------------------|--------------------|
| Kotliar et al.4   | 71  | Male   | Gross hematuria  | Large nodulare  | RC with ileal conduit         | Death after 20 months |
| Braslis et al.2   | 58  | Female | Dysuria          | bladder tumor  | Urethral cyst                  | Pelvic exenteration |
| Braslis et al.2   | 70  | Female | Gross hematuria  | Stenosis lesion of the right upper tract | Right nephro-ureterectomy | Alive after 6 months |
| Yamashita et al.5 | 70  | Male   | Frequency, urgency, anuria | Large bladder mass | RC with ileal conduit | n.a. |
| Isono et al.3     | 69  | Female | Gross hematuria  | Papillary pedunculated bladder tumor | TURBt              | No recurrence after 7 months |
| Our case          | 65  | Male   | Progressive LUTS | Non-papillary pedunculated bladder tumor on the vesical trigonum | RC with ileal conduit | Death after 14 weeks |

RC, radical cystectomy; TURBt, transurethreal resection; LUTS, lower urinary tract symptoms.

Table 2. Microscopic evaluation of each case. Common findings are glycogen-rich cytoplasm and nuclear atypia. In contrast to adenocarcinomas of the bladder glandular differentiation and hobnail cells are not found.

| Report            | Cases | Microscopic findings                                      |
|-------------------|-------|-----------------------------------------------------------|
| Kotliar et al.4   | Case 1| Primarily eosinophilic cytoplasm, small foci of pale cytoplasm, moderate pleomorphism of the nuclei |
| Braslis et al.2   | Case 1| TCC with clear-cell component, cytoplasmic glycogen       |
|                   | Case 2| Clear-cell type TCC                                       |
| Yamashita et al.5 | Case 1| Diffuse clear-cell cytoplasm, severe nuclear atypia, alveolar growth pattern |
| Isono et al.3     | Case 1| Clear-cell cytoplasm                                      |
| Our case          | Case 1| Diffuse glycogen-rich, clear cytoplasm, nuclear atypia, alveolar growth pattern |

TCC, transitional cell carcinoma.

Table 3. Immunohistochemical evaluation of each case. Distinct staining features of clear-cell variant transitional cell carcinomas have yet not been identified. A distinction to prostate cancer and renal cell cancer can be made.

| Report            | Cases | Immunohistochemical staining                                         |
|-------------------|-------|---------------------------------------------------------------------|
| Kotliar et al.4   | Case 1| PAS+, DPAS+, acid mucins-, AE1/AE3+, PSA-, PLAP-, chromogranin-, NSE-PAS+, DPAS+, acid mucins- |
| Braslis et al.2   | Case 2| Mucins-, cytoplasmic glycogens- n.a.                               |
| Yamashita et al.5 | Case 1| CK7+, CK20+, 34BE12+, vimentin, CEA-                              |
| Isono et al.3     | Case 1| CK7+, CK20+, CEA+, vimentin, EMA-, CD10-                          |
| Our case          | Case 1| CK7+, CK20+, CK8/18+, PSA, vimentin, HMB-45-, S-100-, CA-125, melan-A, CD10- |

Figure 1. Computed tomography demonstrating bladder wall thickening (red arrow) but no evidence of perivesical tissue involvement and no evidence of metastasis.
were free from recurrence after 7 and 20 months (Table 1).

In conclusion, clear-cell variant urothelial carcinoma is a rare pathologic finding with a variable clinical course. Adenocarcinoma of the bladder, the major differential diagnosis, can be discriminated by conventional histology and immunohistochemistry. Clear-cell variant urothelial carcinoma shows a glycogen-rich cytoplasm and may be either circumscribed or extensive whereas adenocarcinoma is characterized by glandular differentiation and hobnail cells. Up to date immunohistochemical staining does not help to differentiate both variants (Table 3). Therefore, the pathologist is urged to make a decision based on microscopic findings. Future attempts should strive for strict diagnostic criteria as a prerequisite to define the underlying biology/genetic defects. Larger series are needed to classify prognostic groups and to choose the best therapeutic options for this rare tumor entity.

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