Primary Large-Cell Undifferentiated Carcinoma of the Ureter

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Significance of the Study

- To the best of our knowledge, this is the first case of a large-cell undifferentiated carcinoma of the ureter in the literature. This tumor had an aggressive behavior and the patient had a dismal prognosis.

Keywords

Large-cell carcinoma · Undifferentiated tumor · Hematuria · Liver metastases · Upper urinary tract carcinoma

Abstract

Objective: To report the first case in the literature of a primary large-cell undifferentiated carcinoma (LCUC) of the ureter with a very aggressive behavior and dismal prognosis. **Clinical Presentation and Intervention:** A 60-year-old woman with a history of intermittent macroscopic hematuria and mild to moderate right flank pain was admitted to the Department of Urology. Tissue biopsies and cytological samples were taken. Pathologic examination was consistent with LCUC. **Conclusion:** LCUC of the ureter is an aggressive tumor with a high proliferation index. Patients might be diagnosed at an advanced stage. LCUC must be considered in the differential diagnosis of urinary tract pathologies.

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Introduction

Large-cell undifferentiated carcinomas (LCUCs) mostly originate from the salivary glands and lungs [1, 2]. Primary LCUC of the urinary tract is an extremely rare neoplasm [3] with only a few cases occurring in the bladder [4]. To the best of our knowledge, there is no case of LCUC of the ureter in the literature. We report a case of a primary LCUC of the ureter with a very aggressive behavior and dismal prognosis.

Case Report

A 60-year-old woman with a history of intermittent macroscopic hematuria and mild to moderate right flank pain was admitted to the Department of Urology. Her blood pressure was 115/75 mm Hg and her heart rate was 80 beats per minute. Her medical history included mitral valve replacement and coronary artery bypass graft operation. She had no history of smoking. Her hemoglobin, white blood cell and platelet levels on complete blood count were

Fig. 1. Large undifferentiated tumor cells. **a** Trabecular structures and cells forming small tumor groups under the surface urothelium (hematoxylin and eosine [H&E], $\times 20$). **b** Diffuse distribution of undifferentiated tumor cells (H&E, $\times 40$). **c** Large tumor cells (arrows on the left) and lymphocytes (arrow on the right) (H&E, $\times 40$). **d** Tumor cells infiltrating the muscular propria (arrow) (H&E, $\times 40$).

11.1 g/dL, 8.8 and $370 \times 10^3/\mu\text{L}$, respectively. Results of blood biochemical examination were as follows: international normalized ratio 1.47, creatinine 0.90 mg/dL, estimated glomerular filtration rate 66, aspartate aminotransferase 97 U/L, alanine aminotransferase 68 U/L, γ -glutamyltransferase 1,019 U/L, and alkaline phosphatase 802 U/L.

The urinalysis emphasized the presence of mild leukocyturia (16 leukocytes per high-power field) and hematuria (32 red blood cells per high-power field). No bacteria were observed in urine culture.

Abdominal ultrasonography revealed a grade 2 right ureterohydronephrosis. Contrast-enhanced abdominal computed tomography scan confirmed the ureterohydronephrosis due to a solid, contrast-enhancing and totally obstructing mass in the distal ureter and multiple metastases as big as 6 cm in the liver. Cystoscopic examination revealed that the right ureteric orifice was almost occluded. After the resection of the ureteric orifice, a necrotic and saucy material was drained off from the ureter. Ureteroscopic examination showed a bulky solid lesion obstructing the ureter just 5 cm proximal to the right ureteral orifice, which was covered with a smooth urothelium. Tissue biopsies and cytological samples were taken. Ultrasonography-guided liver biopsies and ureteral tissue biopsies indicated that this was a large-cell undifferentiated tumor.

Microscopic evaluation showed a tumoral infiltration of the lamina propria and the muscularis propria. Also, the lymphovascular spaces were infiltrated by tumor cells. The tumor cells were arranged in nests, cords, and solid islands (Fig. 1a–c). Many apoptotic cells and brisk mitotic figures, including atypical mitosis, were present. Cytological characteristics of the tumor cells were: large round to oval nuclear contour, dispersed chromatin, inconspicuous nucleoli, and high nuclear-to-cytoplasmic ratio (Fig. 1c). Although the immunoprofile of this tumor was positive for pancytokeratin (AE1–AE3) (Fig. 2a), it was negative for neuroendocrine markers such as chromogranin A, synaptophysin, and CD56. In addition, it was negative for CK5–6 (Fig. 2b), which helped to differentiate this tumor from transitional cell carcinoma and squamous cell carcinoma. Nuclear expression of Ki-67 proliferation marker was 80% (Fig. 2c).

She was referred to an oncologist for further treatment and she decided to receive a platinum-based chemotherapy. Ten days after she received the first dose of chemotherapy, she was admitted to our emergency department with hematemesis, melena, and hematuria. She died due to severe and gross bleeding 6 h later at the 3rd month of the initial diagnosis.

Fig. 2. Immunohistochemical staining. **a** Tumor cells demonstrating medium positive staining with pancytokeratin (AE1/ AE3) under the heavy positive stained urothelium [pancytokeratin (AE1/AE3), $\times 20$]. **b** Tumor cells not stained with CK5/6 under the heavy stained basal urothelium (CK5/6, $\times 40$). **c** Proliferation index of the tumor was about 80% (Ki-67, $\times 20$).

Discussion

Bladder cancer is the seventh most commonly diagnosed cancer among men worldwide with an age-standardized rate of 9.0 for men and 2.2 for women per 100,000 people [5]. Urothelial carcinomas constitute over 90% of all bladder cancers followed by squamous carcinoma and adenocarcinomas [4]. Urinary bladder pathologies that do not fit into recognized categories and have histological features of sheets of large polygonal or isolated undifferentiated cells can be defined as large-cell undifferentiated bladder carcinomas (LCUBCs) [4]. Pathological diagnosis is crucial in all malignancies to determine the treatment strategy, to predict the prognosis, and to prepare a follow-up scheme [6].

The incidence of LCUBC is unknown, and a male predominance is apparent similar to large-cell neuroendocrine carcinoma (LCNEC) [4, 7]. The reported age of occurrence was 70 in LCUBC [4]. However, our case was a 60-year-old female.

LCUC has been reported to originate from the lung and salivary glands [1, 2]. To the best of our knowledge, there has only been one published series in the literature concerning LCUBC, which consists of detailed pathological and clinical features of 8 cases [4]. There are no reports on the primary LCUC of the ureter.

In differential diagnosis of LCUC of the urinary bladder and ureter, the other rarely seen tumors such as LCNECs must be considered [8–10]. In some cases of LCUC, the tumor cells are architecturally and cytologically similar to LCNEC as in our case. However, immunohistochemistry showed that LCUC was positive for cytokeratin markers (AE1/AE3 and CK7) and negative for neuroendocrine markers (chromogranin and synaptophysin) [4] as in our case.

LCUBC tends to show an aggressive behavior and is diagnosed at an advanced stage. Almost all patients have lymph node metastases at the time of the diagnosis. Outcome is generally worse than comparably staged and treated conventional high-grade urothelial carcinoma. Lopez-Beltran et al. [4] compared the survival of patients with LCUBC with conventional urothelial carcinoma of similar stages. Univariate survival analyses demonstrate worse outcomes for LCUBC. Most patients (6 of 8) died of their disease after a mean of 10.8 months from diagnosis.

In concordance with the study by Lopez-Beltran et al. [4], our patient was diagnosed at an advanced stage and at the time of diagnosis she had liver metastases. She died due to severe hematuria and gastrointestinal bleeding within 3 months after the diagnosis.

Given the metastatic status of LCUC at diagnosis, curative surgery seems unreasonable. Also, there are no well-established chemotherapy protocols for LCUC of the urinary tract. Considering the origin of this undifferentiated carcinoma, platinum-based chemotherapy regimen such as gemcitabine-cisplatin or paclitaxel-cisplatin might be the treatment of choice.

Conclusion

LCUC of the ureter is an aggressive tumor with a high proliferation index. Patients might be diagnosed at an advanced stage. LCUC must be considered in differential diagnosis of urinary tract pathologies. The description of new cases will improve our knowledge and experience on this little-known entity.

Statement of Ethics

Informed consent was not obtained because the patient died.

Disclosure Statement

The authors declare that there are no conflicts of interest.

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