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Case Report

Clear cell adenocarcinoma of the urinary bladder: a case report and review of literature

Maryam Ahmadi[1], Adam Osman[1], Peng Lee[1,2,3], Fangming Deng[2], Guanghong Liao[3]

[1]Department of Pathology, SUNY Downstate Medical Center, Brooklyn, New York, NY, USA; [2]Department of Pathology, NYU Langone Medical Center, NYU School of Medicine, New York, NY, USA; [3]Department of Pathology and Laboratory Medicine, VA New York Harbor Healthcare System, New York, NY, USA

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Abstract: The most common histological type of urinary bladder cancer is urothelial carcinoma (UC). Clear cell adenocarcinoma (CCA) of the urinary bladder is a rare histologic subtype of adenocarcinoma in the urinary tract. The tumor primarily affects women and has histomorphological features resembling CCA of the female genital tract (or Müllerian origin). Clear cell adenocarcinoma consists of cells with abundant clear cytoplasm, arranged in solid, glandular, or tubulocystic patterns. Patients typically present with gross hematuria, dysuria, and discharge. In this study, we report a case of a 50-year-old male, presenting with gross hematuria, which was subsequently diagnosed with CCA at our pathology department. Furthermore, we provide a short systematic review of the literature for this rare histopathological entity and a brief discussion about its morphological and immunohistochemical (IHC) characteristics.

Keywords: Clear cell adenocarcinoma, urinary bladder

Introduction

Cancer affecting the urinary bladder is a prevailing disease worldwide [1], with epidemiological studies reporting its incidence at 541,000 cases per year globally, and approximately 150,000 deaths per year [2]. The most common histological types of bladder cancer - urothelial carcinoma (UC) and its ten different variants recognized by WHO [3], squamous cell carcinomas, adenocarcinomas, and undifferentiated carcinomas [3] have been extensively described. In contrast, clear cell adenocarcinoma (CCA) of the urinary bladder is a rare neoplasm [1].

CCA was first reported by Dow and Young in 1968 [4]. These tumors contain sheets of uniform ovoid cells with clear cytoplasm containing abundant glycogen [5, 6]. Since there are no distinguishing symptoms of CCA, diagnosis is based on histopathological identification of these characteristics.

CCA usually arises from the female genital tract. Its cytologic and ultrastructural features are similar to those of CCA arising in the female genital tract to suggest its Mullerian differentiation, CCA is sometimes found in the lower urinary tract in women, most commonly involving the urethra, where it may arise in paraurethral ducts or diverticula. In males, the possible theory of origin is glandular differentiation of urothelium.

Case report

A 50-year-old male admitted with complaint of intermittent pelvic discomfort with recurrent blood clots in the urine for last 8 months and history of ED admission 3 month ago for gross hematuria, upper tract infection and episodes of urinary retention. No positive physical signs were found. He has been an active smoker for the past 29 years. Computed tomography (CT) scan revealed diffuse irregular wall throughout the urinary bladder with most pronounced towards the superior bladder. Cystoscopy demonstrated suspicious papillary mass seen on the left lateral/anterior bladder wall with a larger suspicious mass at the bladder neck.

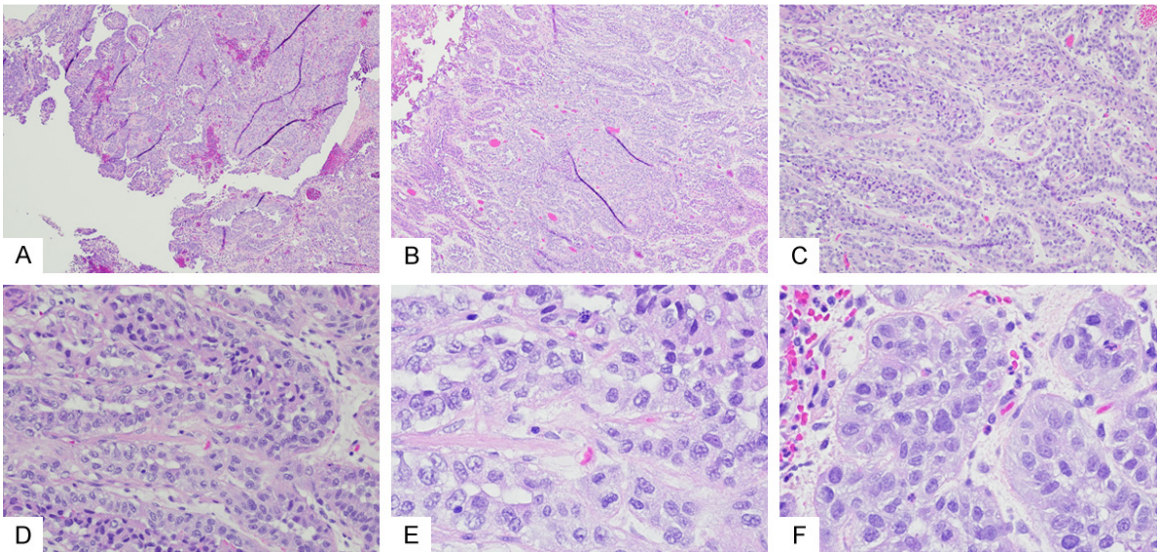

Figure 1. Histology of clear cell adenocarcinoma of bladder. (A-C) Tumor shows papillary and tubular patterns. (D-F) Tumor cells demonstrate nuclei hyperchromacia with prominent nucleoli and clear cytoplasm. Magnification: (A, B) 40×; (C) 100×; (D) 200×; (E and F) 400×.

Transurethral resection of bladder tumor (TURB) was done.

On gross examination, the TURB tissue was fragmented and grayish white, and its texture was soft. On microscopic examination, the tumor showed a prominent papillary growth pattern (**Figure 1A-C**). Most tumor cells were in cuboidal or columnar shape and hobnail cells were seen containing abundant clear cytoplasm and low mitotic activity (**Figure 1D-F**). Tumor cells showed moderate to marked nuclear atypia and only a few mitoses were recognized. A few small pieces of muscularis propria tissue were present which were negative for tumor.

To establish the nature of the tumor cells with clear and vacuolated cytoplasm, immunohistochemical staining was performed. Tumor cells were diffusely positive for PAX8 (**Figure 2A**), AE1/AE3, AMACR (**Figure 2B**), and HNF-1beta (**Figure 2C**) and negative for GATA3 (**Figure 2D**), PSA (**Figure 2E**), NKX3.1, CK7, CK20, CDX2, CA9, and p63 (**Figure 2F**). Based on histological features and IHC profile, the diagnosis of clear cell adenocarcinoma of the urinary bladder was established.

Initially, a tentative plan for TURP and bladder mass removal was made, but the patient was reported with 2 right lung nodules on a chest CT scan in 3 months later. He underwent the surgical resection of the right lung lower lobe, and the lung nodule showed sheets of tumor cells in glandular growth pattern (**Figure 3A** and **3B**), immunohistochemical stains revealed that tumor cells are positive for AMACR (**Figure 3C**), PAX8 (**Figure 3D**), and HNF-1beta (**Figure 3E**), and negative for CK7, GATA3 (**Figure 3F**), p63 and TTF-1, confirming the diagnose of metastatic clear cell adenocarcinoma of the bladder origin. At six months follow-up, the patient was reported to be doing well.

Discussion

Primary CCA of the bladder is a very rare type of bladder cancer that was first reported by Dow and Young in 1968 [4]. The most common locations of the tumor are the posterior wall, trigone, lateral wall, and urethra. Unlike urothelial carcinoma, most CCAs of the bladder are large, solitary masses forming papillary or sessile structures [7]. Cystoscopy is necessary for all patients who were suspected of bladder cancer, including CCA. Because of no specific characteristics for symptoms, signs, and accessory examinations compared with common urothelial carcinoma, clear cell adenocarcinoma is diagnosed mainly on histopathology. The histogenesis of CCA in the bladder remains controversial. In the older literature, tumors mostly were designated “mesonephric adenocarcino-

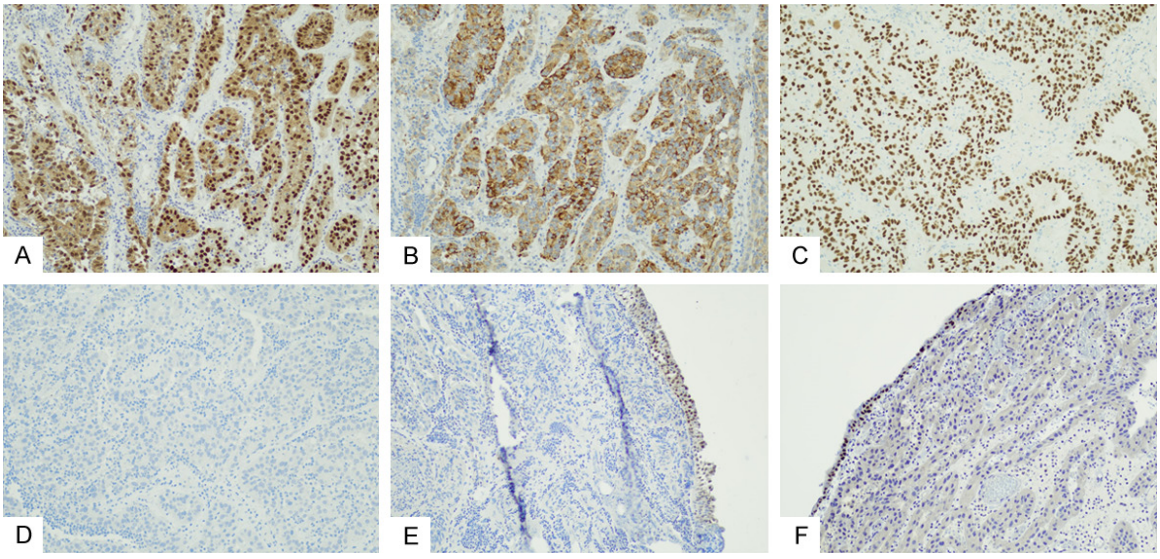

Figure 2. Immunostaining results reveal that tumor cells are positive for PAX8 (A), AMACR (B), and HNF-1beta (C); and negative for PSA (D), GATA3 (E) and p63 (F). Magnification: 100×.

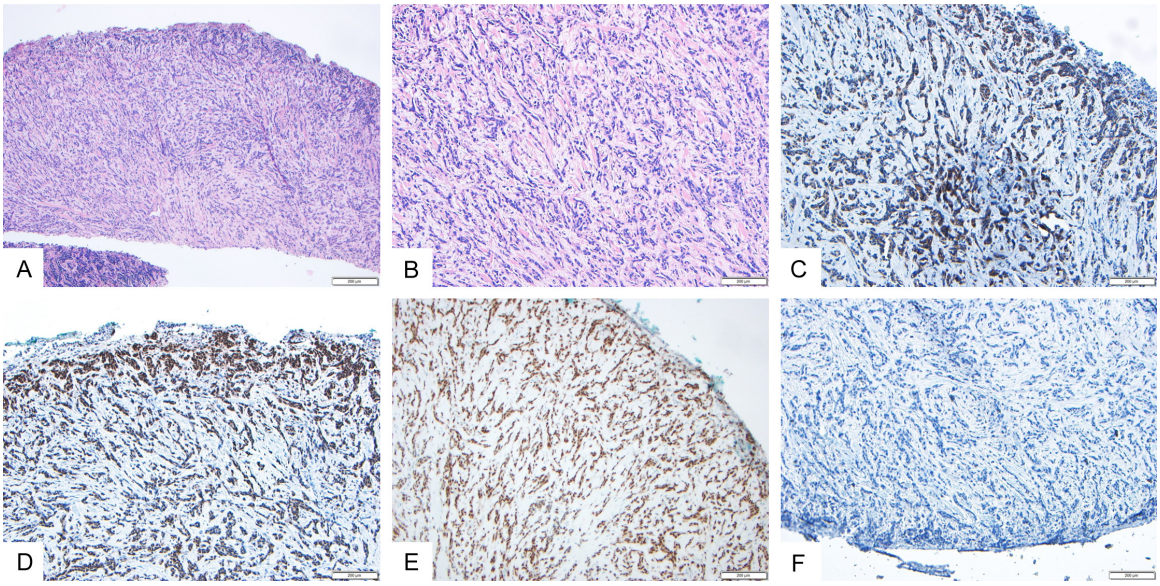

Figure 3. Lung with tumor metastasis. Tumor cells are showing glandular pattern (A and B); they are positive for AMACR (C), PAX8 (D) and HNF-1beta (E) and negative for GATA3 (F), TTF-1 (not shown) and p63 (not shown). Bar = 200 um.

ma", but it lacked convincing evidence for a mesonephric origin [1]. Some authors believe that it arises from Mullerian elements of the bladder and is histogenetically similar to the female genital tract, because in some cases the neoplasms have been associated with vesical endometriosis or have arisen in Mullerian duct cysts or remnants in the bladder [8, 9]. However, a recent study presented evidence for urothelial origin in most clear cell adenocarcinomas of the urinary tract [10, 11] and some studies suggested that CCA may be associated with nephrogenic adenoma because of some similar histological features [10, 11]. CCA is characterized by admixtures of tubular glands, microcysts, papillae and diffuse masses. The cells range from flat to hobnail and cuboidal with abundant, clear and glycogen-rich cytoplasm, often with significant nuclear atypia and mitotic activity [1, 12, 13].

CCA of the renal pelvis is difficult to differentiate from clear cell or papillary RCC and the other types of carcinomas of urothelial origin show clear cell features, which include urothelial carcinoma and adenocarcinoma of non-CCA type [12]. The distinction of CCA from other types of urothelial carcinoma with clear cell features is difficult due to the rarity of CCA in the renal pelvis. Non-CCA types of urothelial carcinoma can be excluded by positive immunoreaction for HNF and PAX8 (or PAX2) [13]. The prognosis of CCA of the bladder remains unclear. It is generally more malignant than common urothelial carcinoma, but more cases and longer follow-up periods are required to elucidate these points. Lymph nodes and bone seem to be the most common metastatic sites for this disease [14, 15].

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Disclosure of conflict of interest

None.

Address correspondence to: Guanghong Liao, Department of Pathology and Laboratory Medicine, VA New York Harbor Healthcare System, 423 East 23rd Street, New York, NY 10010, USA. Tel: 212-686-7500 Ext. 4504; Fax: 212-951-6341; E-mail: guanghong.liao@va.gov

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