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Case Report

Primary small cell carcinoma in the urinary bladder: a case report and review of the literature

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Abstract: Background: Neuroendocrine small cell carcinoma in the urinary bladder is extremely rare in clinical practice. All current research is basically a single center retrospective study or a case report. The prognosis of this kind of disease is really poor and there is still no established diagnosis standard. Case presentation: We report the case of an 88 year-old male patient who had gross hematuria, which had been diagnosed as bladder cancer based on the signs and the history of urothelial carcinoma. Considering the patient's age and quality of life, we made a transurethral resection of the bladder and performed a ureteroscopy, instead of a radical cystectomy. An immunohistochemical analysis indicated it was neuroendocrine small cell carcinoma. Imaging examinations suggested no distant metastasis. After half a month, the patient died from respiratory and circulatory failure. Conclusion: Based on this case, we discuss the pathogenesis, clinical diagnosis, and treatment of small cell neuroendocrine carcinoma in the urinary bladder. It is complex, and the incidence of the disease is very low. As for us, with more clinical research, we believe the guidelines for the diagnosis and treatment of this disease will gradually develop in the future.

Keywords: Neuroendocrine small cell carcinoma, urinary bladder, clinical treatment

Background

Neuroendocrine small cell carcinoma in the urinary bladder is extremely rare in clinical practice. Studies have shown that small cell carcinoma of the bladder makes up only 0.35-0.7% of all malignant bladder tumors [1-4]. This type of carcinoma is characterized by a very high degree of malignancy, rapid progress, early metastasis, and poor prognosis. After Cramer reported the first case in 1981 [5], major medical research centers all around the world began to study this carcinoma. However, because it is extremely rare, all current research is basically done as a single-center retrospective study or a case report. The guidelines of urology do not explicitly mention the gold standard for the treatment of the disease at this time. Therefore, further research on neuroendocrine small cell bladder cancer is very necessary. This case study focuses on neuroendocrine small cell carcinoma of the bladder, its pathological features, and clinical treatments.

Case presentation

An 88-year-old male patient presenting with gross hematuria for 2 weeks was hospitalized in The Fourth Hospital Affiliated to China Medical University on December 13, 2017. Gross hematuria is painless and contains blood clots. The patient had a history of hypertension for 50 years which was controlled by medicine. Laboratory examinations showed: red blood cells in urine, 166.5/HPF; white blood cells in urine, 97.9/HPF. The patient did not have a history of smoking or drinking. None of the patient's family members had been admitted to the hospital because of bladder cancer. A computerized tomography (CT) urography showed that an irregular mass was located in the right posterior side of the bladder which had invaded the bilateral ureters (**Figure 1A**) and led to the dilatation of the proximal ureter and renal pelvis (**Figure 1B**). Imaging examinations suggested there was no distant metastasis. We considered it to be T3aN0M0. In May 2014, he underwent a transurethral resection of the bladder. The po-

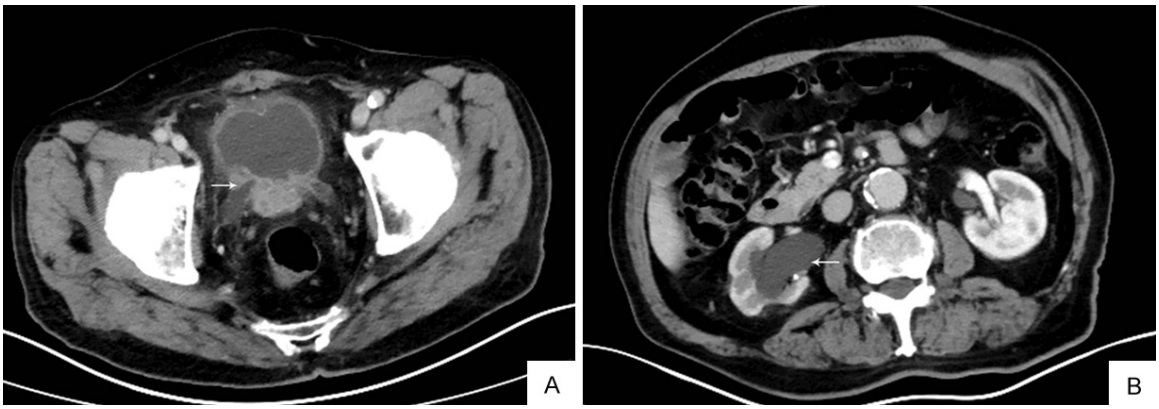

Figure 1. A. Computed tomography urography shows an irregular mass was located in the right posterior side of the bladder, which also shows an invasion of the bilateral ureters. B. The mass led to the dilatation of the proximal ureter and renal pelvis.

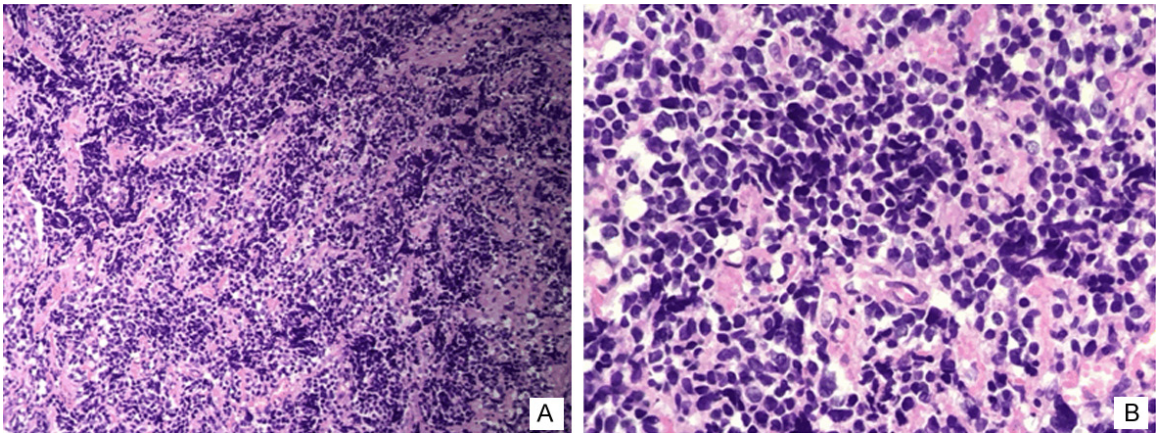

Figure 2. Histopathologic. HE, (A) ×200; (B) ×400.

stoperative pathology indicated urothelial carcinoma. After surgery, he had regular chemotherapy with gemcitabine. The above signs and the history led to the suspicion of a recurrence of bladder tumor.

Considering that the tumor had invaded muscle tissue, we recommended that the patient undergo radical cystectomy. However, the patient and his family did not agree with this plan because of his age and quality of life. On December 15, 2017, a transurethral resection of the bladder was carried out. We used a laser to cut the tumor and then indwelled a double-J stent in the both ureters to prevent ureteral obstruction. The surgical samples were formalin fixed, paraffin embedded, and cut into 4-micron thick sections for the histological examination with hematoxylin-eosin stain (**Figure 2**) and immunohistochemical procedures against CgA, Syn, CK7, CK20, P63, P16, GATA3 and Ki-67. The immunohistochemical analysis was positive for Syn(++), CgA(++), P16(++), GATA3(+), and Ki-67 (+80%) tumor cells (**Figure 3**) but negative for CK7, CK20, and P63. A high proliferation index (80%) was documented against Ki-67 staining (**Figure 3**), indicating the malignant property of the lesion. It turned out to be neuroendocrine small cell carcinoma. On December 27, 2017, the patient died from respiratory and circulatory failure.

Discussion

It is well-known that small cell carcinoma generally originates in the lungs and that small cell bladder carcinoma is the most common small cell carcinoma outside of the lungs [6, 7]. There are 3 origin theories of small cell carcinoma of the bladder: Bladder neuroendocrine cell malig-

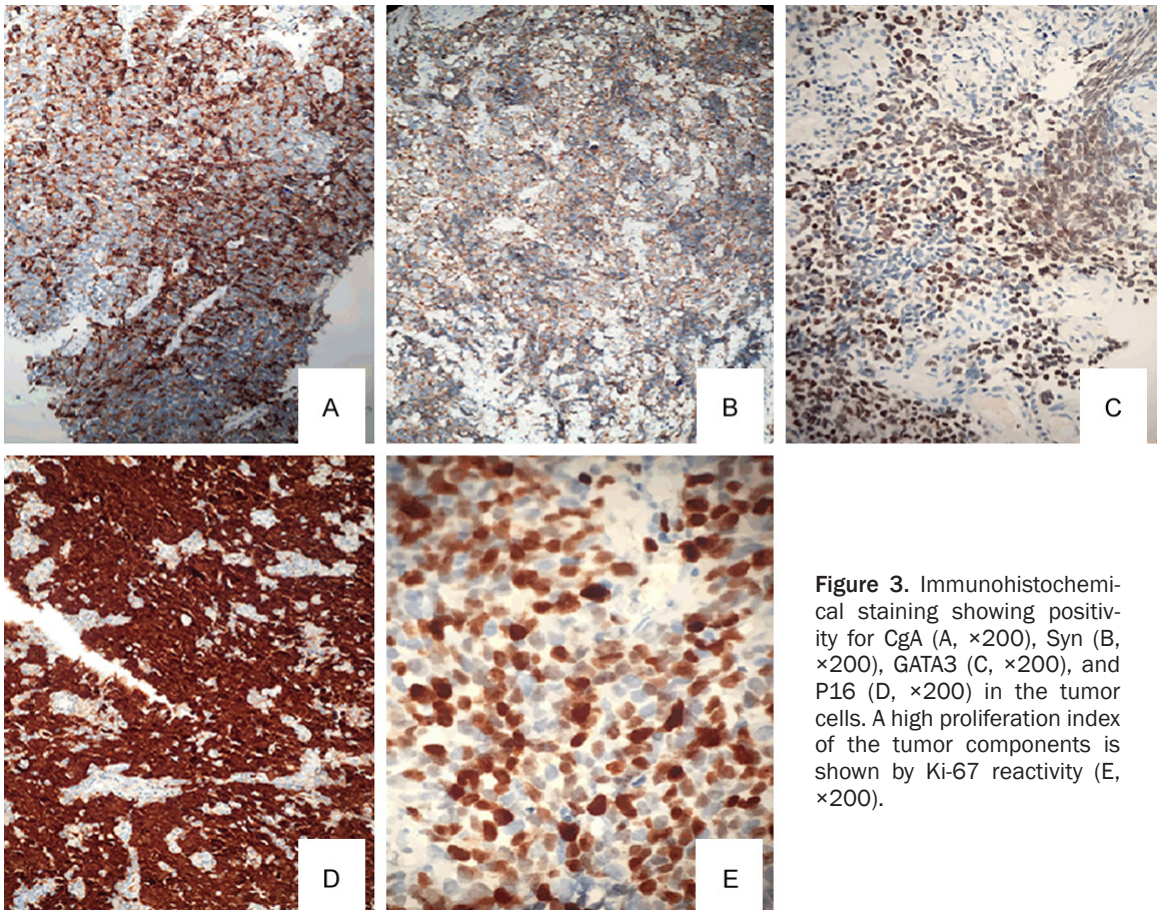

Figure 3. Immunohistochemical staining showing positivity for CgA (A, ×200), Syn (B, ×200), GATA3 (C, ×200), and P16 (D, ×200) in the tumor cells. A high proliferation index of the tumor components is shown by Ki-67 reactivity (E, ×200).

nant transformation, stem cell origin, and urothelial cell metaplasia [8]. As relevant research progresses, the stem cell origin hypothesis is the most accepted among researchers [9, 10]. That is, bladder small cell carcinoma and bladder epithelial cancer have the same origin. A recent article pointed out that small-cell carcinoma of the urinary bladder shares a common clonal origin with conventional urothelial carcinoma and may arise from a heterogeneous subclone [11]. Under normal circumstances, small cell carcinoma of the bladder appears with other types of cancer at the same time and the most common accompanying cancer is urothelial carcinoma. The primary isolated small cell carcinoma of the bladder is only about 12% to 32% [4, 12]. The source of bladder endocrine neuroendocrine carcinoma in this case may be of urothelial origin GATA3(+) and of neuroendocrine differentiation Syn(++) CgA(++). GATA3 may be linked to the tumor origin. 32% of nuclear GATA3 expression was found in bladder small cell carcinoma and 13% in lung small cell carcinoma [13]. Another interesting point is that patient's examination did not find any distant metastasis, which is different from the early metastasis of small cell carcinoma of the bladder. In 2014, this patient had a TURBT because of urothelial carcinoma.

Clinically, the disease is usually in a relatively progressive stage when it is discovered. The most common symptom is painless gross hematuria and the second most common symptom is dysuria and bladder irritation [2-4, 8, 14]. The incidence rate in males is significantly higher than it is in women. Related studies have shown that the ratio is generally 3:1-5:1 [2-4, 8, 15]. The diagnosis of small cell carcinoma of the bladder mainly depends on immunohistochemistry. The immunophenotype usually expresses Syn and CgA, and it also expresses CK, EMA, CK7, p53, CD117, Ki-67 and so on. Related studies have found that serum NSE detection is also helpful in the diagnosis of small cell carcinoma, which may be an independent prognostic factor for small cell carcinoma of the bladder [16, 17]. A recent article also

Table 1. Worldwide clinical research on small cell bladder cancer over a decade

Journal	NO	TNM	Surgery	BI	CT	RT	Conclusion
Fisher Valuck, et al. Eur Uro Focus, 2017	225	T1-4aN0M0			YES		Treatment effect: RC & CT>CT; CRT>CT; RC & CT with CRT (P>0.05)
	203	T1-4aN0M0			YES	YES	
	201	T1-4aN0M0	RC		YES		
Zhi Chen, et al. WJSO, 2017	1	T4aN2M0	RC			YES	Death
	3	T2b-4N0-1M0	RC		YES		1 Of 3 survival
	4	T2-3bN0M0	PC	YES			2 Of 4 survival
Jung K, et al. Clin Genitourin Cancer, 2017	20		RC after NCT		NCT		NCT can downstage
Patel SG, et al. J Urol, 2014	174	cTis-cT4, cN0 or cM0	PC				NCT followed by RC had the most favorable survival
	333	cTis-cT4, cN0 or cM0	PC	MT	MT	MT	
	46	cTis-cT4, cN0 or cM0	RC				
	72	cTis-cT4, cN0 or cM0	RC	MT	MT	MT	
Sakatani T, et al. Hinyokika Kiyo, 2014	3	T1-3N0M0	RC & NCT		NCT		NCT followed by RC could cure patients with small cell carcinoma of the bladder without metastatic disease
	5	T1-3N0M0	OT	OT	OT	OT	
Sioghan P. Lynch, et al. Eur Uro, 2013	48	Tx-4aN0M0	RC after NCT		NCT		The group with NCT prognosis better
	47	Tx-4aN0M0	RC				
Richard P Meijer, et al. Int JU, 2013	50	Tx-4N0-1M0	TURBT		NCT	YES	CT help prognosis; Response to NCT represents prognosis factor
	16	Tx-4NxM1/Tx-4N2-3M0	RC		YES	YES	
Perán Teruel M, et al. Arch Esp Urol, 2012	2	T2-4N2M0-1	RC/TURBT		CT	RT	2 Of 11 survival
	2	T2-4N2M0-1	RC/TURBT		CT		
	7	T2-4N2M0-1	RCTURBT				
Mukesh M, et al. BJU Int, 2009	3		RC		YES		The response rate to CT is high but the overall prognosis is poor
	1					YES	
	6				YES	YES	
MARCUS L. QUEK, et al. J Uro, 2005	3	T0-2N0M0					CT improved survival compared with cystectomy alone
	2	T3-4N0M0					
	15	T1-4N(+)M(+)					
Nicolas W, et al. Cancer, 2005	12	T2N0M0	RC/PC/TURBT/RC after NCT		YES		CT should be a platinum-based; RC except when metastatic disease is present
	13	T3N0M0	RC/PC/RC after NCT/RC after RT		YES	YES	NCT should be considered in T3-4 disease
	19	Tx-4NxM0-1	RC/RC after NCT/RC after RT		YES	YES	

Abbreviations: BI, bladder irrigation; NCT, neoadjuvant chemotherapy; CT, chemotherapy; RC, radical cystectomy; RT, radiotherapy; PC, partial cystectomy; CRT, chemoradiotherapy; MT, multimodal treatment; OT, other treatment.

found that the higher serum LDH levels than normal also indicate a poor prognosis [18]. The secondary evaluation of the disease mainly depends on cystoscopy, urinary CT, ultrasound, and so on. One case reported that contrast-enhanced ultrasound has a high diagnostic value for small cell carcinoma of the bladder [19]. When the disease is found, it is generally in a progressive stage. Early detection, early diagnosis and more comprehensive secondary examination methods are very important.

At present, the treatment of the disease is surgery combined with radiotherapy and chemotherapy. Surgical methods are generally TURBT, partial cystectomy, radical cystectomy, cystectomy, and some other treatment methods. And some studies have reported that TURBT with chemotherapy also has a good prognosis in the early stage of cancer [20, 24]. In terms of chemotherapy, related studies have shown that cisplatin is the main chemotherapy drug [4]. Some researchers have also suggested that the treatment plan should draw from the treatment of lung small cell carcinoma [21]. So far, no unified conclusion has been reached. Some researchers recommend the use of berubicin, methotrexate, vinblastine, cisplatin, or some other drugs in clinical practice [22, 23]. Neoadjuvant chemotherapy also has a very significant effect on the prognosis of the disease [4, 24-27]. Due to the extremely low incidence of the disease, there are no available treatment guidelines at this time. The study of small cell carcinoma of bladder by urological research centers around the world consists only of some single-center retrospective studies and case reports. The limited number of cases makes it difficult to formulate a reliable gold standard for treatment. Here is a review of clinical research data over a decade: (**Table 1**) [4, 7, 14, 24, 26-32]. From **Table 1**, we can conclude that surgery combined with chemotherapy is still the main method of treating the disease. In 2005, cisplatin had been proposed as a cornerstone for chemotherapy, but the chemotherapy drugs chosen by different centers vary. Preoperative neoadjuvant chemotherapy can reduce tumor staging and contribute to a better prognosis. Radiotherapy combined with chemotherapy and surgery combined with chemotherapy was superior to mono-chemotherapy, but the effects of the two combination treatments did not show statistical differences. From **Table 1**, we can find that the universe of current clinical research data is still relatively small and there is no conclusion we can draw based on between the various studies.

Conclusion

Using this case as a point of departure, we discussed the pathogenesis, clinical diagnosis, and treatment of small cell neuroendocrine carcinoma of bladder from 1981 to 2017. It is complex, and the incidence of the disease is very low. As for us, with more clinical research, we believe the guidelines for the diagnosis and treatment of this disease will gradually develop in the future.

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Written informed consent was obtained from the patient for the publication of this case report and the accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal.

Disclosure of conflict of interest

None.

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