

Cases – Clear-cell urothelial carcinoma of the bladder

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Introduction

Variety in histology in urothelial carcinoma of the bladder is often associated with advanced stage at presentation and poor prognosis. Clear-cell is a rare histological variant of urothelial carcinoma of the bladder, with only 22 cases reported in current literature. Most cases reported have resulted in poor prognoses despite aggressive management.¹⁻¹⁷ The two cases described in this report add to the sparse literature regarding clear-cell urothelial carcinoma (CCUC) of the bladder and expand on possible management options for treatment.

Case 1

A 78-year-old female was involved in a fall resulting in a pathological fracture of her right greater trochanter as a consequence of diffuse sclerotic bony metastases. She was a former smoker with a 25 pack-year history. She had no occupational exposures and no family history of cancer.

Computed tomography (CT) revealed a subtle nodule within the right aspect of the urinary bladder, and a large right adnexal mass causing mild right hydronephrosis (Fig. 1A). Urine cytology collected was negative. She had previously been followed by a urologist for intermittent gross hematuria, however, there was no evidence of bladder cancer at her most recent cystoscopy performed eight months prior at the time of ureteroscopy for nephrolithiasis. Evaluation for gynecological and gastrointestinal malignancies were also negative.

Repeat CT 12 weeks later showed progression of the bladder mass and right hydronephrosis (Fig. 1B). Flexible cystoscopy revealed a contracted bladder with three large, nodular, bladder tumors near the level of the trigone (Fig. 2A). The right ureteral orifice could not be identified due to distortion of the bladder. Transurethral resection of bladder tumor (TURBT) was performed three weeks later, where the tumors could not be completely resected due to their large size. Histopathological evaluation showed high-grade urothelial carcinoma with invasion of muscularis propria (pT2) with a large portion containing clear-cell variant (Fig. 3).

Following multidisciplinary discussion, plans for palliative chemotherapy (gemcitabine and cisplatin) and radiotherapy were made. Progressive malignancy halted the initiation of systemic chemotherapy. She passed away shortly afterwards secondary to metastatic disease.

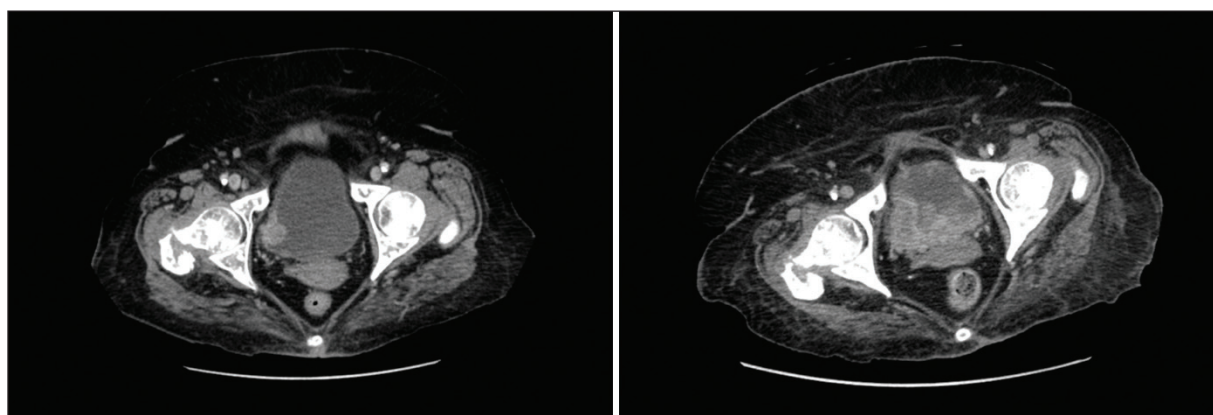


Fig. 1. (A) Initial axial computed tomography (CT) scan showing a subtle nodule within the right aspect of the urinary bladder (Case 1) and **(B)** followup CT showing significant disease progression (Case 1).

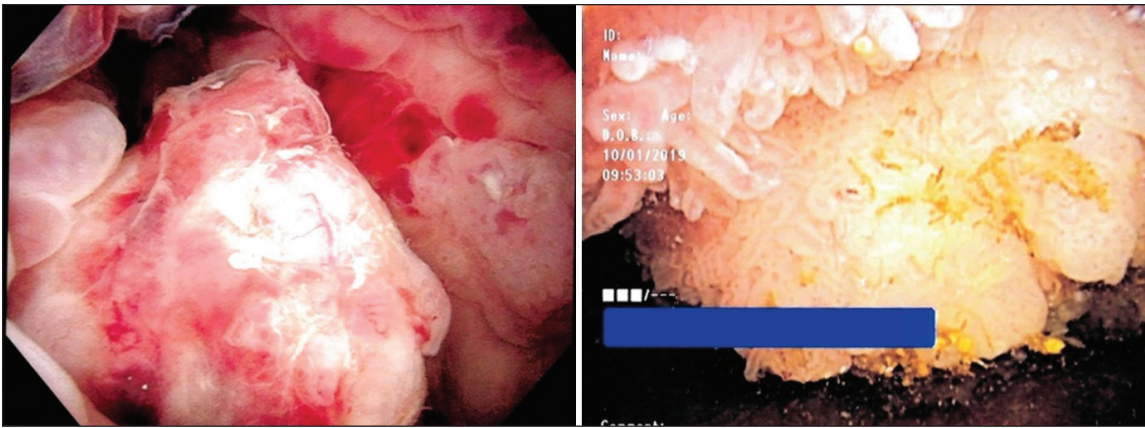


Fig. 2. Cystoscopic appearance of clear-cell urothelial carcinoma; both demonstrating multifocal masses with poor differentiation (**A**: Case 1; **B**: Case 2).

Case 2

An 83-year-old female presented to urology clinic after an incidental 3.6 cm bladder tumor and left hydronephrosis were found on CT during evaluation for diarrhea. She had no lower urinary tract symptoms or gross hematuria. Her brother had bladder cancer requiring radical cystectomy; a number of other malignancies existed in her family, including colon, stomach, and kidney cancer. She was a former cigarette smoker with >50 pack-year history. She had no occupational exposures. Metastatic workup demonstrated multiple sub-centimetre pulmonary nodules felt to be non-malignant. Flexible cystoscopy identified multiple large, left-sided bladder tumors; the left ureteric orifice could not be identified (Fig. 2B).

During TURBT, multiple large bladder tumors were resected, as well as the left ureteric orifice. Urine cytology was collected from the left ureter and a ureteric stent was inserted. Urine cytology from this ureteral washing was negative. Pathology demonstrated high-grade non-muscle-invasive papillary urothelial carcinoma (pTa) with clear-cell variant.

She underwent repeat TURBT for evaluation of residual disease. Histological evaluation was negative for malignancy. Repeat ultrasound demonstrated resolution of left hydronephrosis. She completed intravesical bacillus Calmette-Guérin (BCG) induction but developed recurrent bladder tumors at three months, located away from the original resection site. The pathology of this was non-invasive papillary urothelial carcinoma (pTa) with carcinoma in situ. She underwent a repeat induction course of BCG and has been on maintenance BCG for six months with no evidence of recurrence.

Discussion

CCUC is a relatively new diagnosis of the urinary bladder, first described in 1995, and added to the WHO classification of tumors of the urinary system in 2016.^{1,18} There appears to be a predisposition to the male sex (83.3%), with only four cases reported in females. The average age of patients at time of diagnosis is 70.5 years old (range 43–85) and hematuria is the most common presenting symptom (72.7%) (Table

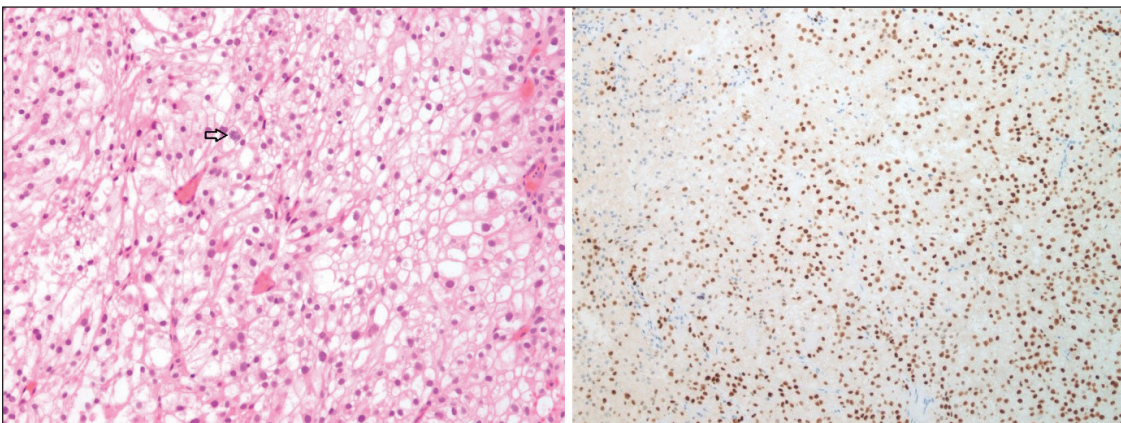


Fig. 3. Pathologic images of clear-cell urothelial carcinoma from Case 1. (**A**) Representative focus (200x objective) of the tumor illustrating abundant clear cytoplasm and nuclear pleomorphism associated with poor papillary architecture consistent with clear-cell variant. An abnormal mitotic figure is seen at the center. (**B**) Nuclear immunostain for p63 confirms the diagnosis of clear-cell variant and demonstrates prominent variability in the nuclear features.

Table 1. Reports of clear-cell urothelial carcinoma of the urinary bladder

No.	Reference	Age/sex	Presenting symptom(s)	Tumor stage	Management	Outcome & followup
1	Kotliar et al ⁵	71/M	Gross hematuria	pT3	RC + PLND and chemotherapy	Death after 20 months
2	Braslis et al ⁶	70/M	Frequency, urgency, anuria	pT2	RC + PLND	NR
3	Yamashita et al ⁷	70/M	Gross hematuria	pT2	TURBT	Alive and no recurrence after 7 months
4	Isono et al ⁸	69/F	Gross hematuria	pTa	TURBT	Alive and no recurrence after 20 months
5	Kramer et al ⁹	65/M	Progressive lower urinary tract symptoms	pT4	RC + PLND	Death after 14 weeks
6	Persec et al ¹⁰	72/M	Gross hematuria	pTa	TURBT	Recurrence after 3 months
7	Zhang et al ¹¹	65/M	Gross hematuria	NR	TURBT and intravesical chemotherapy*	Alive at 15 months
8	Klimis and Dellaportas ¹²	78/M	Gross hematuria	pT2	TURBT	Alive after 6 months
9	Lum ¹³	68/M	NR	pT3	RC + PLND	Recurrence after 8 months
10	Tyritzis et al ¹⁴	NR/M	NR	pT4	RC + PLND	NR
11	Knez et al ¹⁵	75/M	Gross hematuria	pT3	RC + PLND	Alive at 10 months
12	Mihai et al ¹	81/M	Gross hematuria and acute urinary retention	pT3	RC + PLND	Death after 5 months (bone metastasis)
13	Rotellini et al ¹⁶	82/M	Asymptomatic	pT2	RC + PLND	Alive at 12 months
14	Mai et al ³	68/M	Previous low-grade urothelial cancer	pT3	RC + PLND	Alive at 12 months
15		75/M	Gross hematuria	pT3	RC + PLND	Alive at 2 years
16		55/M	Gross hematuria	pT3	RC + PLND	Alive at 2 years
17		78/M	Gross hematuria	pT3	RC + PLND	Death after 1 year
18		85/M	Gross hematuria	pT4	None due to advanced disease	Death after 1 year
19	Kumar et al ²	50/M	Gross hematuria	pT2	RC + PLND	Death after 4 months
20	Blackmur et al ⁴	43/F	Gross hematuria	pT1	PC + PLND	Alive and no recurrence at 45 months
21		73/M	Gross hematuria	pT4	Aborted RC, chemotherapy, salvage immunotherapy, palliative radiotherapy	Alive at 45 months
22	Bosoteanu et al ¹⁷	68/M	Gross hematuria, urinary retention	pT3	RC + PLND	Death after immediate postoperative complications
23	Case 1	78/F	Pathological fracture	pT2	TURBT, palliative radiotherapy	Death after 4 months
24	Case 2	83/F	Asymptomatic	pTa	Repeat TURBT, induction (x2) and maintenance BCG	Recurrence following initial induction BCG. Alive at 17 months, recurrence-free on maintenance BCG following repeat induction

*Intravesical pirarubicin (40 mg). BCG: intravesical bacillus Calmette-Guérin; NR: not reported; PC: partial cystectomy; PLND: pelvic lymphadenectomy; RC: radical cystectomy; TURBT: transurethral resection of bladder tumor.

1). Although clear-cells can be seen in the microscopic evaluation of other urothelial carcinomas, CCUC consists predominantly or exclusively of clear-cells, representing the extreme end of clear-cell tumors.¹⁹ Differential diagnosis includes clear-cell adenocarcinoma of the urinary bladder and metastatic clear-cell renal cell carcinoma.¹

Previously reported cases of CCUC were found to be associated with aggressive clinical courses (Table 1). Most bladder tumors presented with muscle invasion (82.6%); one-year overall survival was 52.9% among those with >1 year followup and reported mortality outcomes. Four patients

(16.7%) presented with metastatic disease at the time of presentation, most commonly to the lung and bones, and two patients (8.3%) developed rapid progression following radical cystectomy. For patients with muscle-invasive CCUC, reported treatments included TURBT and radical cystectomy with or without adjuvant chemotherapy (Table 1). When adjuvant systemic chemotherapy was used, cisplatin was preferred over carboplatin for better tumor response and survival, and was used in combination with gemcitabine.⁴ In cases of muscle-invasive CCUC, we recommend multidisciplinary assessment for consideration of neoadjuvant or

adjuvant chemotherapy, in addition to radical cystectomy and lymphadenectomy in suitable patients, in accordance with Canadian Urological Association (CUA) and American Urological Association guidelines (AUA).^{20,21}

Only three cases of non-muscle-invasive CCUC had been described prior to this report (Table 1). Reported treatment options for this group included TURBT^{10,11} with or without intravesical chemotherapy,¹¹ and partial cystectomy with lymphadenectomy⁴ (Table 1). The effectiveness of intravesical chemotherapy for patients with non-muscle-invasive urothelial carcinoma with variant histology is unknown. In case 2 presented in this report, we identified mixed response to intravesical BCG, with early solitary recurrence following induction and sustained short-term recurrence-free interval following repeat induction and maintenance BCG. This report is the first to describe the use of intravesical BCG in non-muscle-invasive CCUC. Based on this finding and reports from the literature, we suggest that repeat TURBT should be performed following initial TURBT for pTa CCUC to minimize the risk of understaging, remove residual disease, and improve efficacy of intravesical therapy, given the aggressive nature of this disease. Following repeat TURBT, intravesical BCG can be considered to potentially reduce the risk of recurrence and progression, though the efficacy of BCG is unknown in clear-cell histology. Disagreement exists as to whether patients with variant histology have poorer²² or superior²³ response to intravesical BCG compared to conventional high-grade urothelial carcinoma. In the setting of pT1 CCUC, however, early radical cystectomy with lymphadenectomy is the recommended treatment option according to the CUA and AUA guidelines.^{20,21}

Conclusions

Clear-cell urothelial carcinoma is a rare histological variant of bladder cancer with poor prognosis. The preferred treatment choice for tumors with invasion of the lamina propria or muscularis propria is radical cystectomy. Multidisciplinary assessment is necessary for consideration of platinum-based neoadjuvant or adjuvant chemotherapy for patients suitable for radical cystectomy. Based on our experience, TURBT with intravesical BCG for non-invasive papillary disease can be used. Further reporting of the clinical outcomes of this rare histological variant will aid in identifying patients who may be suitable for bladder-sparing approaches.

Competing interests: The authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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