

Cases – Clear-cell urothelial carcinoma of the bladder

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Introduction

Variant histology in urothelial carcinoma of the bladder is often associated with advanced stage at presentation and poor prognosis. Clear-cell is a rare histologic 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.^{2,5-20} 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 pathologic 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 (Figure 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 (Figure 1B). Flexible cystoscopy revealed a contracted bladder with three large, nodular, bladder tumours near the level of the trigone (Figure 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 large size. Histopathologic evaluation showed high-grade urothelial carcinoma with invasion of muscularis propria (pT2) with large portion containing clear-cell variant (Figure 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.

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 (Figure 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. Histologic 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 3 months, located away from original resection site. The pathology of this was non-invasive papillary urothelial carcinoma (pTa) with carcinoma of situ. She underwent a repeat induction course of BCG and has been on maintenance BCG for 6 months with no evidence of recurrence.

Discussion

Clear-cell urothelial carcinoma (CCUC) is a relatively new diagnosis of the urinary bladder, first described in 1995, and added to the WHO classification of tumours of the urinary system in 2016.^{2,3} 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 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 tumours.⁴ Differential diagnosis include clear-cell adenocarcinoma of the urinary bladder and metastatic clear-cell renal cell carcinoma.²

Previously reported cases of CCUC were found to be associated with aggressive clinical courses (Table 1). Most bladder tumours presented with muscle invasion (82.6%); 1-year overall

survival was 52.9% among those with >1 year follow-up 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 is utilized, cisplatin was preferred over carboplatin for better tumour response and survival and is used in combination with gemcitabine.⁷ 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 CUA and AUA guidelines.^{21,22}

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^{13,14} with or without intravesical chemotherapy,¹⁴ and partial cystectomy with lymphadenectomy⁷ (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 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 whether patients with variant histology have poorer²³ or superior²⁴ response to intravesical BCG compared to conventional high grade urothelial carcinoma. In the setting of pT1 CCUC, however, it is clear that early radical cystectomy with lymphadenectomy is the recommended treatment option according to the CUA and AUA guidelines.^{1,25}

Conclusions

Clear-cell urothelial carcinoma is a rare histologic 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 noninvasive papillary disease can be utilized. Further reporting of the clinical outcomes of this rare histologic variant will aid in identifying patients who may be suitable for bladder-sparing approaches.

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Figures and Tables

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).

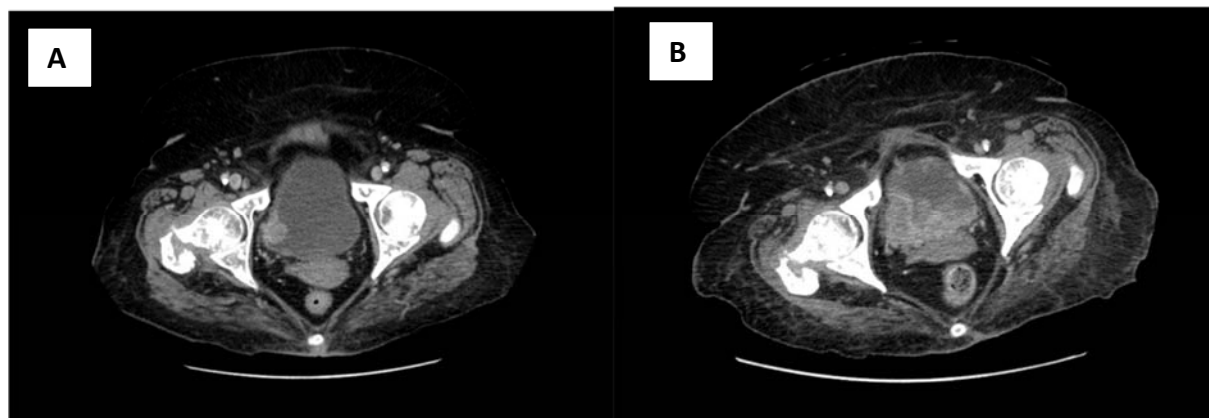


Fig. 2. Cystoscopic appearance of clear-cell urothelial carcinoma; both demonstrating multifocal masses with poor differentiation (A: Case 1; B: Case 2).

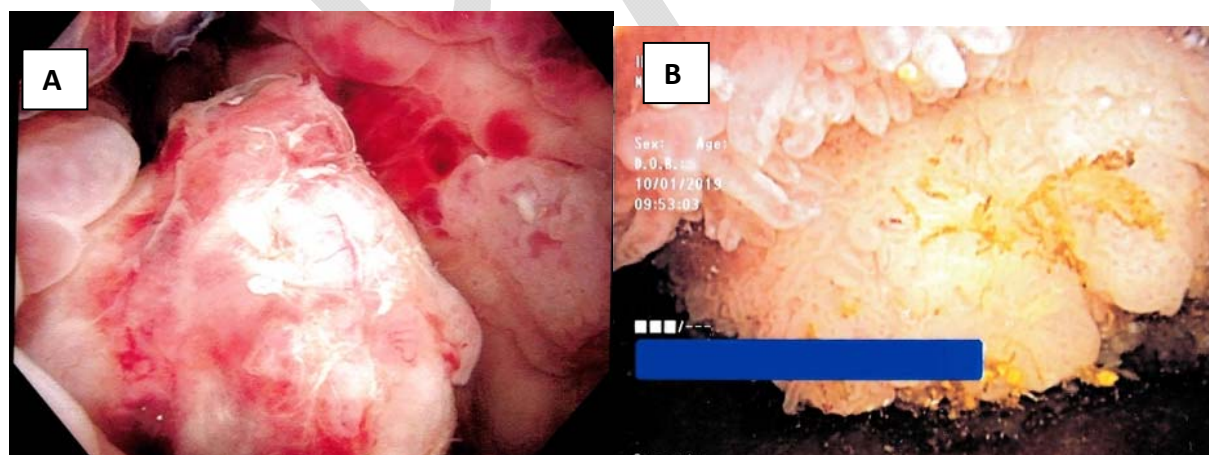


Fig. 3. Pathologic images of clear-cell urothelial carcinoma from Case 1. **(A)** Representative focus (200x objective) of the tumor illustrating abundant clear cytoplasm and nuclear pleomorphism associated with poor papillary architecture consistent with clear-cell variant. An abnormal mitotic figure 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.

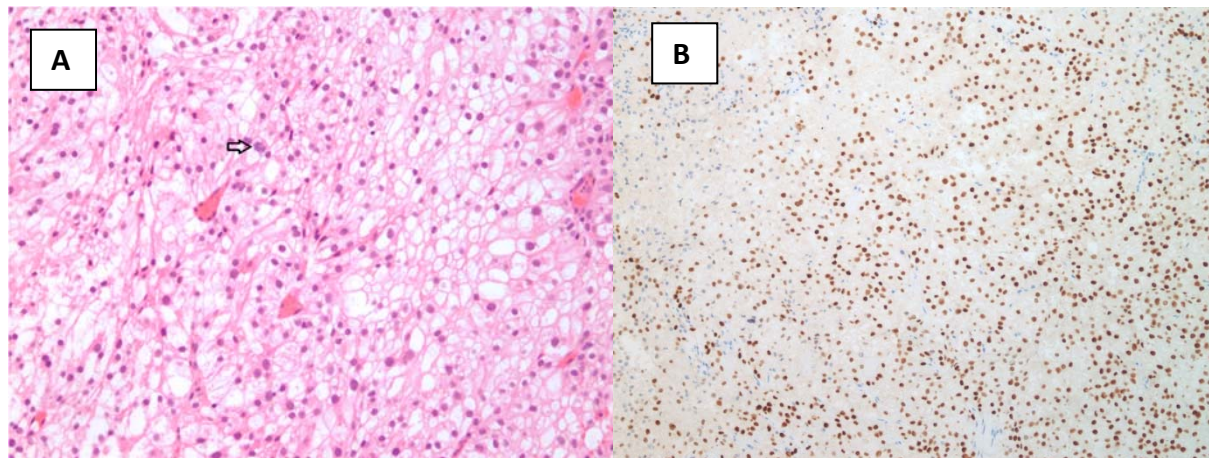


Table 1. Reports of clear-cell urothelial carcinoma of the urinary bladder						
No.	Reference	Age/sex	Presenting symptom(s)	Tumor stage	Management	Outcome & followup
1	Kotliar et al ⁸	71/M	Gross hematuria	pT3	RC + PLND and chemotherapy	Death after 20 months
2	Braslis et al ⁹	70/M	Frequency, urgency, anuria	pT2	RC + PLND	NR
3	Yamashita et al ¹⁰	70/M	Gross hematuria	pT2	TURBT	Alive and no recurrence after 7 months
4	Isono et al ¹¹	69/F	Gross hematuria	pTa	TURBT	Alive and no recurrence after 20 months
5	Kramer et al ¹²	65/M	Progressive lower urinary tract symptoms	pT4	RC + PLND	Death after 14 weeks
6	Persec et al ¹³	72/M	Gross hematuria	pTa	TURBT	Recurrence after 3 months
7	Zhang et al ¹⁴	65/M	Gross hematuria	NR	TURBT and intravesical chemotherapy*	Alive at 15 months
8	Klimis and Dellaportas ¹⁵	78/M	Gross hematuria	pT2	TURBT	Alive after 6 months
9	Lum ¹⁶	68/M	NR	pT3	RC + PLND	Recurrence after 8 months
10	Tyritzis et al ¹⁷	NR/M	NR	pT4	RC + PLND	NR
11	Knez et al ¹⁸	75/M	Gross hematuria	pT3	RC + PLND	Alive at 10 months
12	Mihai et al ²	81/M	Gross hematuria and acute urinary retention	pT3	RC + PLND	Death after 5 months (bone metastasis)
13	Rotellini et al ¹⁹	82/M	Asymptomatic	pT2	RC + PLND	Alive at 12 months
14	Mai et al ⁶	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 ⁵	50/M	Gross hematuria	pT2	RC + PLND	Death after 4 months
20	Blackmur et al ⁷	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. ²⁰	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	Dead 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-Guerin; NR: not reported; PC: partial cystectomy; PLND: pelvic lymphadenectomy; RC: radical cystectomy; TURBT: transurethral resection of bladder tumor.