Non-muscle-invasive clear cell carcinoma of the urinary bladder: Is cystectomy necessary?

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BMJ Case Reports CP 2019;12:e226928.

Non-Muscle Invasive Clear Cell Carcinoma of the Urinary Bladder – Is Cystectomy Necessary?

Journal:	*BMJ Case Reports*
Manuscript ID	bcr-2018-226928.R1
Manuscript Type:	Rare disease
Date Submitted by the Author:	n/a
Complete List of Authors:	Jayawardhana, Tamani; Darent Valley Hospital, Urology & Nephrology Alsayed, Hossam; Dartford and Gravesham NHS Trust, Urology Goel, Amit; Maidstone Hospital Madaan, Sanjeev; Darent Valley Hospital, Urology & Nephrology
Keywords:	Urological cancer < Oncology, Pathology, Urological surgery < Surgery

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TITLE OF CASE

Non-Muscle Invasive Clear Cell Carcinoma of the Urinary Bladder – Is Cystectomy Necessary?

SUMMARY ***Up to 150 words summarising the case presentation and outcome (this will be freely available online)***

We report the clinical presentation, histological findings and management of a 49 years old female patient with non-muscle invasive clear cell carcinoma of the urinary bladder. In the literature there are only 7 such case reports. We feel that transurethral resection of the bladder tumour followed by close cystoscopy surveillance is a suitable management for non-muscle invasive clear cell carcinoma of the urinary bladder.

BACKGROUND ***Why you think this case is important – why did you write it up?***

Clear cell carcinoma (CCC) of the bladder is a very rare variant of bladder tumours. There are very few cases reported in the literature. The majority of the reported cases are muscle invasive CCC of the bladder treated mainly with cystectomy. Although no consensus is currently agreed regarding treatment of CCC of the bladder, we feel that transurethral resection of the tumour (TUBT) followed by close cystoscopy surveillance and upper tract imaging is a suitable management option for non-muscle invasive CCC of the urinary bladder.

CASE PRESENTATION ***Presenting features, medical/social/family history***

A 49-year-old fit and well female patient presented to urology rapid access service with painless haematuria in October 2014. She reported no other urinary tract symptoms. She had no significant comorbidities and was not on any medications. There was no family history of any urological malignancy.

INVESTIGATIONS ***If relevant***

Flexible endoscopic examination revealed a solid lesion approximately one centimetre in size at the dome of the bladder [Figure 1]. An urgent TURBT was performed. Multiple tumour fragments measuring approximately 45x55x5 mm in aggregate were sent for histology. Microscopy showed fragments of moderately differentiated CCC of the bladder, with tubulo-cystic spaces lined by cells with abundant clear cytoplasm. No urothelial differentiation was seen and no in-situ component was identified. The tumour was invading the lamina propria, but not the deep muscle present in the sample. No vascular invasion was seen [Figure 2]. Immunohistochemistry showed strong CK7 staining and high proliferation index. WT1, vimentin, CK20 and CDX2 were negative. There was some weak patchy CD10 staining and the tumour was PAX-8 positive & GATA-3 negative. The profile favoured a bladder origin for this tumour [Figure 3-5]. The final tumour staging was G3pT1N0M0 as further imaging showed no evidence of distant metastasis or lymphadenopathy

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DIFFERENTIAL DIAGNOSIS ***If relevant***

The most common malignancy of the bladder epithelium is urothelial carcinoma followed by squamous cell carcinoma and adenocarcinoma. Clear cell carcinoma mainly affects the kidneys.

TREATMENT ***If relevant***

After discussion of the management options, which included total cystectomy, partial cystectomy and cystoscopic surveillance at the multidisciplinary meeting the consensus was to offer surveillance cystoscopy and upper tract imaging.

OUTCOME AND FOLLOW-UP

A follow-up cystoscopy done 3 months after the initial TURBT showed a recurrence similar in size to the initial tumour in the right anterior wall adjacent to the bladder neck. The suspicious area was resected and microscopic examination showed sheets of cells with occasional gland formation showing abundant clear cytoplasm infiltrating into the lamina propria confirming a recurrence of the clear cell adenocarcinoma. There was no lymphovascular or muscle invasion seen. The immunohistochemistry results obtained were similar to the initial tumour and additionally stained negative for P504S too. The options of cystectomy and periodic cystoscopic surveillance were once again discussed and cystoscopic surveillance was agreed upon as the path of management for the future. Since then the patient has been disease free for 45 months at time of submission of this article.

DISCUSSION ***Include a very brief review of similar published cases***

Primary CCC is a rare bladder tumour. Dow and Young [1] first reported a case in 1968 since which there have been a total of 49 cases reported including the case presented in this paper. In the literature the following suggestions have been made regarding the origin of clear cell bladder carcinoma [2]:

a) Originates from the mullerian system in the urinary bladder

b) Is an adenocarcinoma of non mullerian origin that has features of CCC

c) Is a variant of urothelial carcinoma which has undergone glandular differentiation

Some authors have referred to CCC as mesonephroid carcinoma and adenocarcinoma of the bladder despite lack of clear evidence of the definite origin of the tumour. The tumour was referred to as clear cell carcinoma as it appeared similar to the clear cell adenocarcinoma originating from the female genital tract and a few cases have been reported to be associated with endometriosis or remnants of the mullerian duct. A review done by Olivia et al., in 2002 showed that 9 out of 13 patients did not have a tumour associated with endometriosis or any mullerian remnants and four of the tumours showed foci of transitional cell carcinoma [3]. The majority of the cases of CCCs discussed in the literature show a tumour un-associated with endometriosis. This in combination with the findings of the case review done by Olivia et al., and the tumour occasionally occurring in males favours the clear cell carcinoma to be a gland differentiation of urothelial carcinoma [3].

The prognosis of CCC of the bladder is not well understood as it is a rare tumour and the follow

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up post treatment has mostly been less than five years [2]. Surgery, which involves cystectomy, has been the primary method of treatment of clear cell bladder carcinoma as it is mostly diagnosed when the tumour is in its advanced stages.

The current case was diagnosed at an early stage, with invasion only into the lamina propria but no invasion into the muscle wall. Sun et al., in 2008 reported 3 cases that were positive for the marker P504s and have shown the presence of this protein in tumours that are of high grade and stage. The tumour we resected was negative for P504s further confirming its superficial nature [4].

Stage 1 tumours represent non-invasive tumours limited to the lining of the bladder wall with no muscle invasion. The details of these along with the present case have been summarised in the Table 1 [5,6,7,8,9].

There have been 7 cases of non-muscle-invasive CCC reported in the literature. Of these, 43% of patients (3/7) have been treated by TURBT alone, 43% of patients (3/7) were treated with radical cystectomy and 14% of patients (1/7) have been initially treated with TURBT followed by chemotherapy [2].

Table -1: Summary of case reports of superficial CCC of the bladder (Ref 5-9.

Case Reference	Age	Sex	Site	Treatment	Outcome
Doddamani et al., [5]	80	Female	Not available	TURBT followed by repeat TURBT and chemotherapy with carboplatin and methotrexate	No evidence of disease at 3 months post repeat TURBT +chemotherapy
Young and Scully [6]	78	Female	Trigone	TURBT	No evidence of disease at 4 years.
Drew et al., [7]	78	Female	Not Available	Radical Cystectomy	No evidence of disease at 12 months
Drew et al., [7]	50	Male	Not Available	TURBT, Radical cystectomy	Alive with progression of disease at 63 months
Drew et al., [7]	43	Male	Not Available	TURBT	No evidence of disease at 30 months
Lum et al [8]	68	Male	Not available	TURBT	No evidence of disease at 8 months of follow up
Chor et al., [9]	35	Female	Posterior wall	Radical cystectomy	Not Available
Current Case	49	Female	Dome of bladder	TURBT followed by TURBT after 3 months	No evidence of disease at 33 months

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

1- Clear cell carcinoma of the bladder is a very rare form of bladder tumour commonly affecting females.
2- There is no current consensus for treatment of non-muscle invasive CCC of bladder tumour.
3- Primary TURBT followed by surveillance flexible cystoscopy and staging imaging can be offered in patients with non-muscle invasive CCC of the bladder.

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REFERENCES ***Vancouver style (Was the patient involved in a clinical trial? Please reference related articles)***

References:

1. James A.Dow, John D.Young. Mesonephric adenocarcinoma of the bladder. Journal of urology. [Online] 1986;Vol 100(Issue 4): pp. 466-469. Available from: https://doi.org/10.1016/S0022-5347 (17)62554-0 [Accessed 3 April 2018].

2. *Venyo, a k-g. Primary Clear Cell Carcinoma of the Urinary Bladder. Scholarly Research Notices. [Online] 2014;(593826): . Available from: https://doi.org/10.1155/2014/593826 [Accessed 3 May 2018].*

3. *Oliva E, Amin MB, Jimenez R, Young RH. Clear cell carcinoma of the urinary bladder: a report and comparison of four tumours of mullerian origin and nine of probable urothelial origin with discussion of histogenesis and diagnostic problems. Am J Surg Pathol. [Online] 2002; 26(2): 190-197. Available from: https://insights.ovid.com/pubmed?pmid=11812940 [Accessed 16 April 2018]*

4-Sun K, Huan Y, Unger PD. Clear cell Adenocarcinoma of urinary bladder and urethra: Another urinary tract lesion immunoreactive for P504S. Arch Pathol Lab Med. 2008 Sep;132(9): 1417-1422

5. Doddamani D, Ansari MS, Gupta NP, Aron M, singh I, Datta Gupta S. Mesonephroid adenocarcinoma of the bladder and urethra: a case report. Int Urogynecol J Pelvic Floor Dysfunct. 2002; 13(1): 47-9.

6. Young R.H. and Scully R.E**.** *Clear cell adenocarcinoma of the bladder and urethra: A report of three cases and review of the literature*, American journal of surgical pathology. 1985, Vol. 9, pp. 816-826.

7. P.A. Drew, W.M. Murphy, F.Civantos et al. *The histogenesis of clear cell adenocarcinoma of the lower urinary tract: case series and revew of the literature.* Human pathology, 1996, Vol. 27, pp. 248-252.

8. Lum, D. 2006, *Clear cell carcinoma of the urinary bladder* . Pathology 2006 Aug; 38(4):367-70.

9. Chor PJ1, Gaum LD, Young RH. *Clear cell adenocarcinoma of the urinary bladder: report of a case of probable müllerian origin*. Mod Pathol. 1993 Mar;6(2):225-8.

FIGURE/VIDEO CAPTIONS ***figures should NOT be embedded in this document***

Table 1: Summary of case reports of superficial CCC of the bladder.

Figure 1. Flexible cystoscopy appearance of the bladder tumour
Figure 2. Clear cell lining with abundant clear cytoplasm (H&E 40X).
Figure 3. Immunohistochemistry showing PAX-8 positivity in tumour cells (10X).
Figure 4. Immunohistochemistry showing strong CK 7 positivity in tumour (4X).
Figure 5. Immunohistochemistry showing GATA-3 positivity in lining urothelium and negative in tumour cells (10X).

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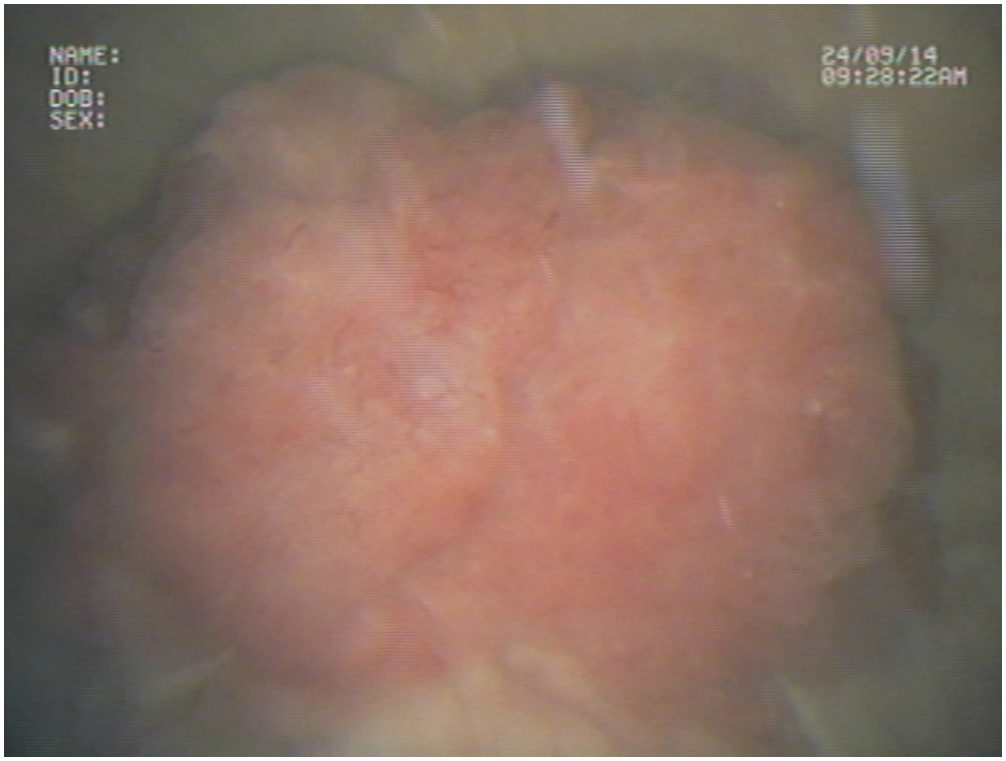

Figure 1. Flexible cystoscopy appearance of the bladder tumour

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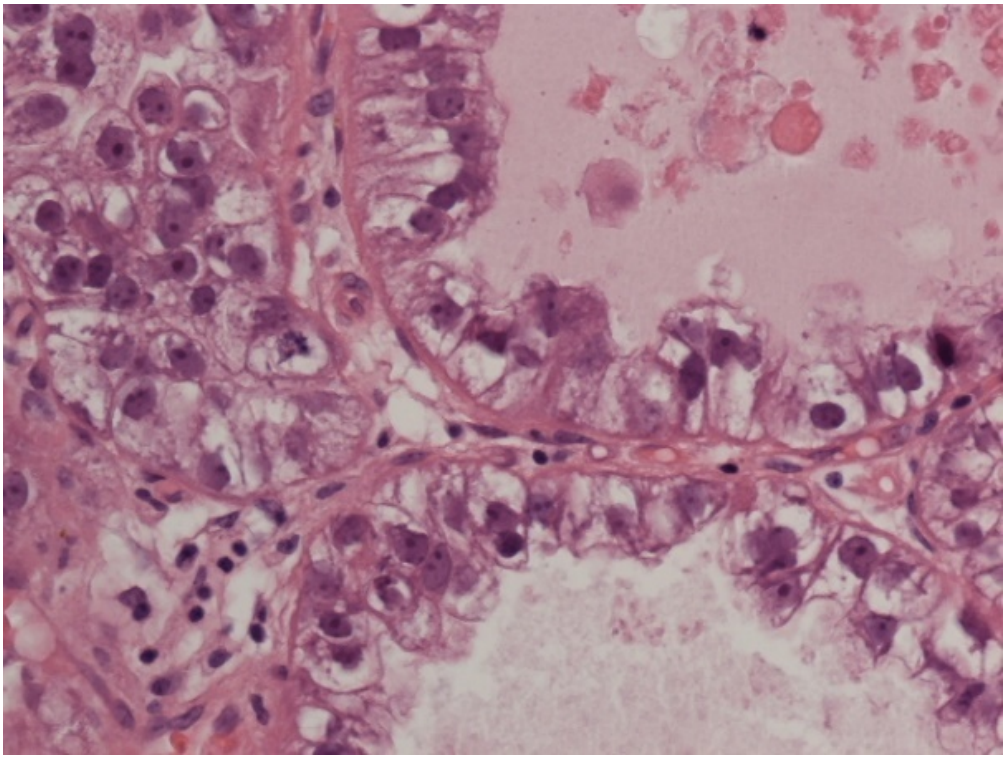

Figure 2. Clear cell lining with abundant clear cytoplasm (H&E 40X).

51x38mm (300 x 300 DPI)

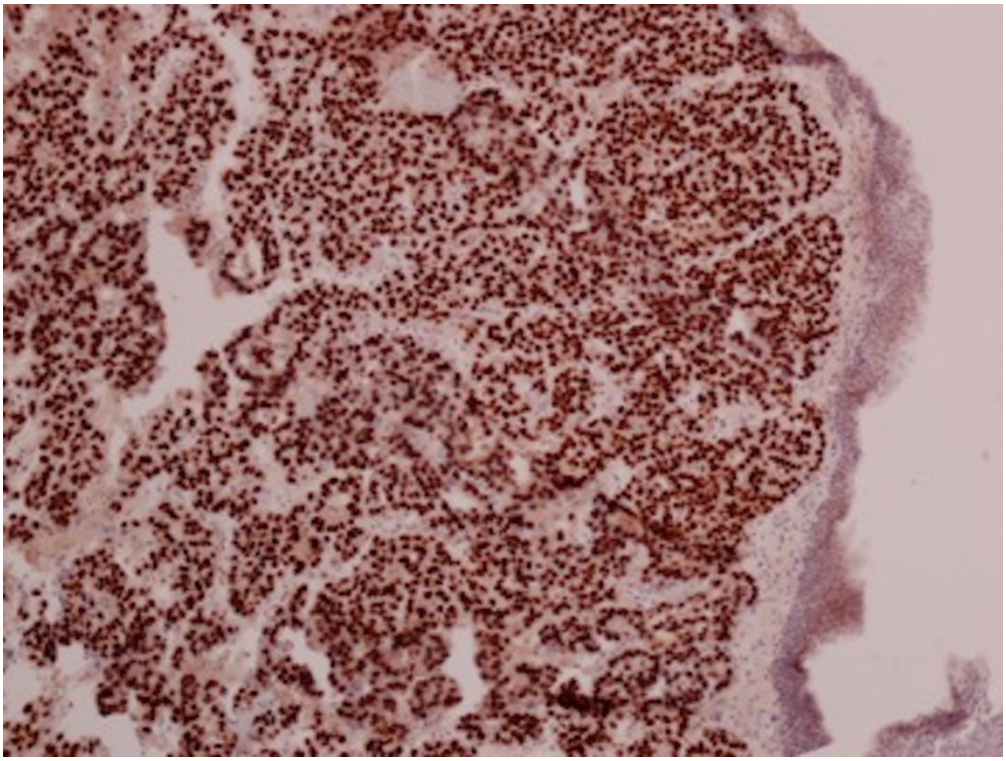

Figure 3. Immunohistochemistry showing PAX-8 positivity in tumour cells (10X).

127x95mm (300 x 300 DPI)

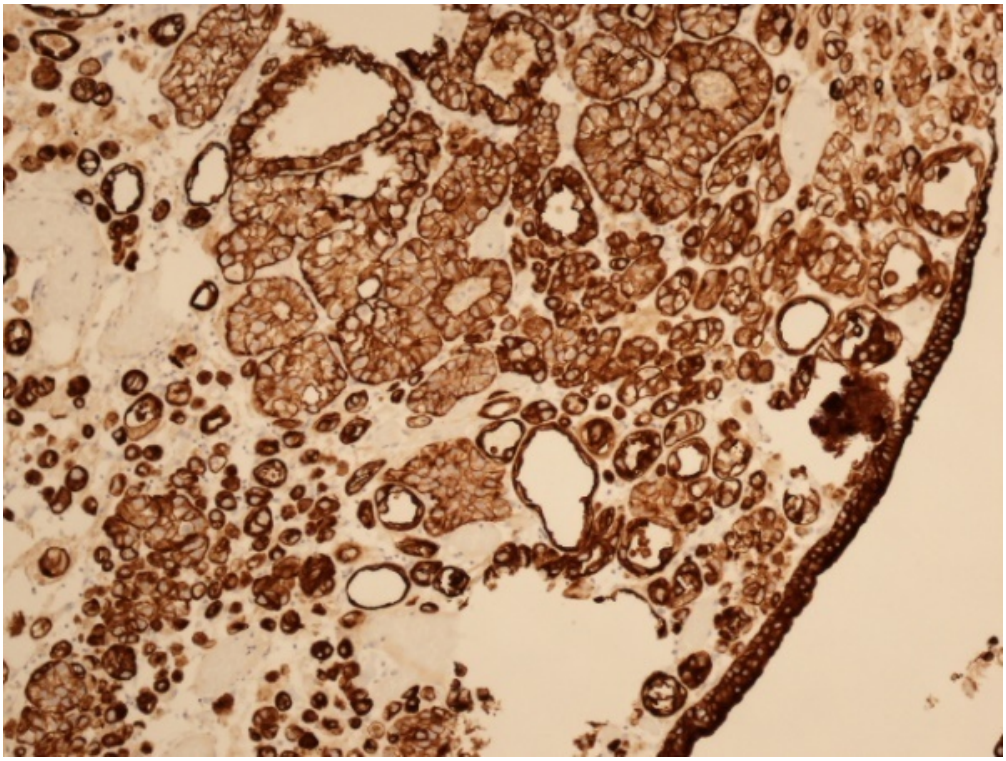

Figure 4. Immunohistochemistry showing strong CK 7 positivity in tumour (4X).

50x38mm (300 x 300 DPI)

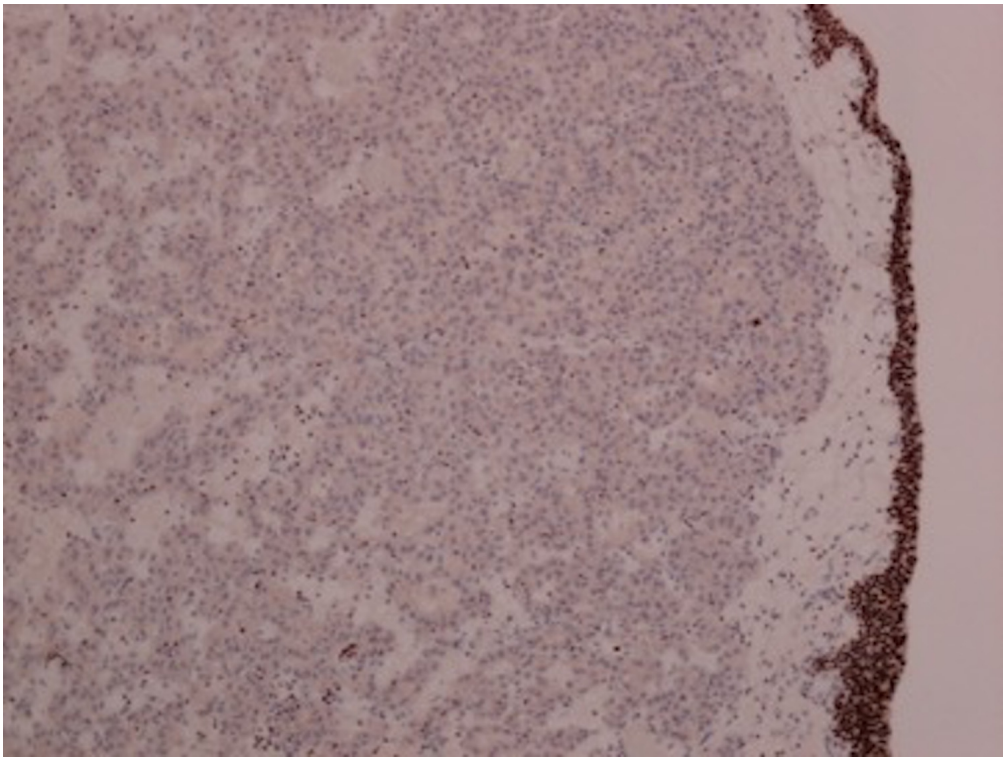

Figure 5. Immunohistochemistry showing GATA-3 positivity in lining urothelium and negative in tumour cells (10X).

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