Case Report

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Clear cell carcinoma of the urinary bladder, case report and literature review

Z. Hashemi[1*], KJ Lentjes[1], D Houtsma[2], R Natté[3] and H Roshani[1]

[1]*Department of urology, Haga teaching hospital, The Hague, The Netherlands*

[2]*Department of oncology, Haga teaching hospital, The Hague, The Netherlands*

[3]*Department of pathology, Haga teaching hospital, The Hague, The Netherlands*

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*Corresponding Author

* Z Hashemi, Department of urology, Haga teach-ing hos-pital, The Hague, The Neth-erlands, Tel: +31 0648783278, E-mail: zahra_mitra@hotmail.nl

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Abstract

Primary clear cell carcinoma (CCC) is a rare type of malignancy occasionally found in the urinary bladder. While CCC is common and histologically similar to the neoplasm in the female genital tract; the histogenesis and biological behavior of this neoplasm, specifically in the bladder, has not yet been thoroughly investigated or understood. Standard treatment options have also not been established, due to lack and sparsity of available research. We present a case of clear cell carcinoma of the urinary bladder in an 81-year-old woman with pelvic lymph nodal and lung metastases.

Keywords: Clear cell carcinoma; Clear cell adenocarcinoma; Mesonephroma; Urinary bladder; Urology

Introduction

The transitional cell carcinoma (urothelial cell carcinoma) is the most common malignancy of the urinary bladder. Other major types include squamous cell carcinoma and adenocarcinoma. Primary clear cell carcinoma (CCC) is a rare entity in the bladder with less than 100 cases reported in current literature (see table 1).

Table 1: Relevant articles retrieved on PubMed for CCC of the urinary bladder

42 case reports/series[1-42]	Alvarez et al. [3]
	A case report of CCC unsuccessfully treated with chemotherapy.
	Hartmann, Arndt et al. [4]
	A case revealing CCC can be a progression of nephrogenic metaplasia.
	Terada, Tadashi [5]
	An autopsy case where the cytoplasm of the CCC of the bladder was free from glycogen and mucins.
	Marchalik, Daniel et al. [6]
	A 26-year-old woman with Prune belly syndrome, cloacal anomaly and uterus didephys, who developed CCC of the bladder.
	Jassim, Sarmad H et al. [7]
	A case with concordant primary CCC of the bladder and primary lung adenocarcinoma with clear cell features.
	Diaz, Edward C et al. [8]
	An 8-year-old girl with primary CCC of the bladder. Good oncologic results with partial cystectomy.
	Lu, Ji et al. [9]
	A 68-year-old female with primary CCC of the bladder, who received intravesical therapy with mitomycin after TURB. Multiple tumor recurrences after therapy lead to the conclusion that intravesical therapy after TURB is not useful.
6 review articles [43-48]	Chan, Erica On-Ting et al. [47]
	The most recent systematic review, which shows 70 cases of clear cell carcinoma in current literature. Articles up till July 2020 were collected.
2 original articles [49-50]	Zhou et al. [49]
	CCC has a poorer prognosis compared to other bladder carcinomas due to higher tumor staging at diagnosis.
	Oliva, Esther et al. [50]
	The presence of CCC in the male population and its immunohistochemistry staining for CK7 and CK20, argues in favor of the hypothesis that CCC emanates from a peculiar form of gland differentiation in transitional (urothelial) cell carcinoma.

Case report

An 81-year-old female with a history of endometriosis, hysterectomy and unilateral oophorectomy presented to the GP with abdominal complaints, gross hematuria, and general fatigue. A CT scan of the abdomen was performed which revealed a 5 x 6 x 4.5 cm tumor in the dorsal aspect of the bladder (Figure 1). As a result, the patient was referred to the gynecologist. Digital vaginal exam revealed a normal vaginal sac and transvaginal ultrasound confirmed a tumor solely in the dorsum of the urinary bladder. The patient was referred to the urology out-patient clinic. Cystoscopy showed that the tumor was located in the trigone and the bladder neck.

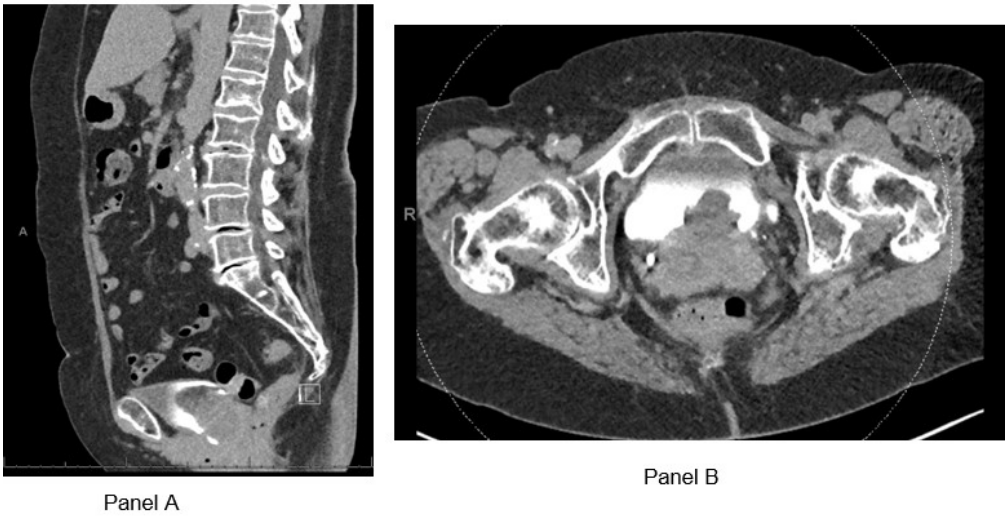
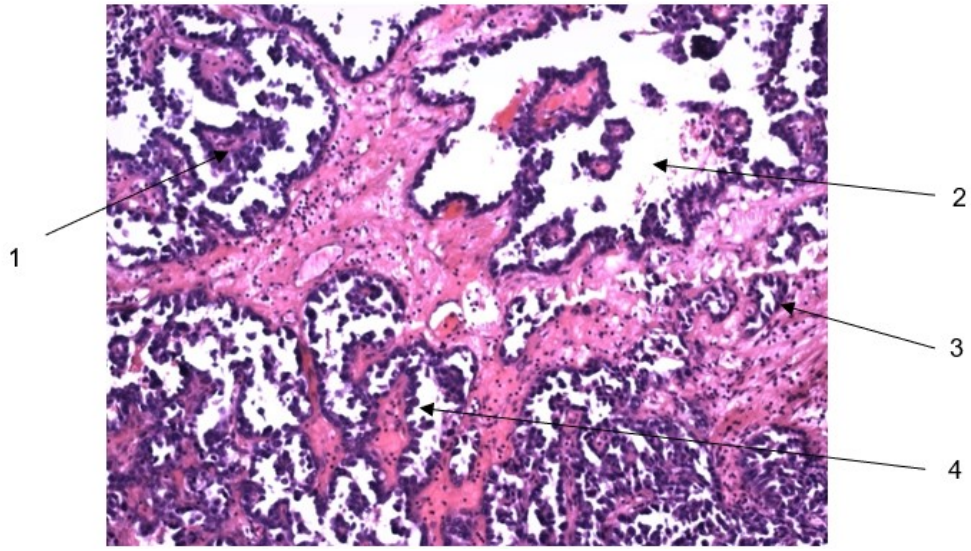


Figure 1: Abdominal sagittal (Panel A) and axial (Panel B) view of the CT scan shows an infiltrative mass located in the bladder dorsally. Margins are blurry and difficult to distinct.

The tumor mass was resected using transurethral resection (TUR); however, the TUR was incomplete due to the tumor size and its extension outside the bladder margins. Histopathology revealed a papillary proliferation of atypical cubic cells with large bulging hyperchromatic nuclei, as well as tubule-cystic structures with hobnail type epithet-lium and solid sheets (Figure 2). The supplemental immunohistochemistry was positive for keratin 7, HNF-1Beta, Naspin and PAX 8, while negative for keratin 20, p63, ER, PR, WT-1, GATA-3, CDX2, TTF-1 and p40. P53 showed wild type expression.



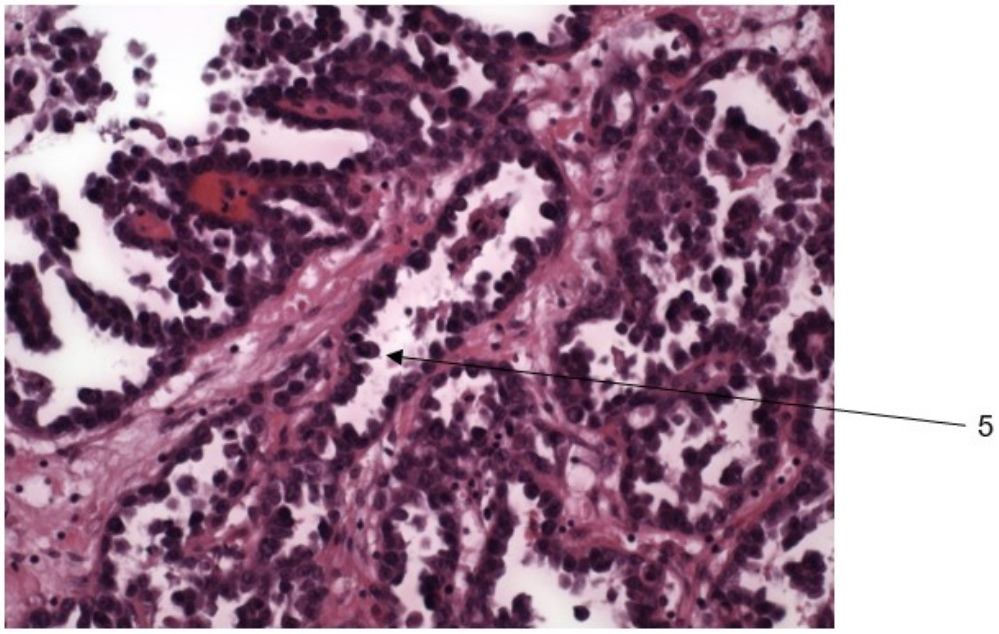


Figure 2: Papillary (arrow 1), tubulo-cystic (arrow 2) and tubular (arrow 3) structures of hobnail epithelial cells with luminally protruding hyperchromatic nuclei and a modest degree of eosinophilic cytoplasm (arrow 4 & 5). (H&E, 100X).

An FDG-PET scan (Figure 3) was performed, which revealed lymphadenopathy of the right iliac region and perirectal fat. A small lung metastasis in the right lower lobe was also discovered. Imaging showed no involvement of the vaginal sac and there was no sign of invasion from outside the bladder. As stated above, the patient had undergone hysterectomy and unilateral ovariectomy in the past. Collectively, patient history, physical examination and histopathological results confirmed the diagnosis of primary clear-cell carcinoma of the bladder.

Palliative treatment options with chemo- and/or radiotherapy were discussed with the patient; given the metastasis, curative treatment was not an option. The patient initially opted for a wait-and-see policy, however four months after diagnosis decided for euthanasia route instead.

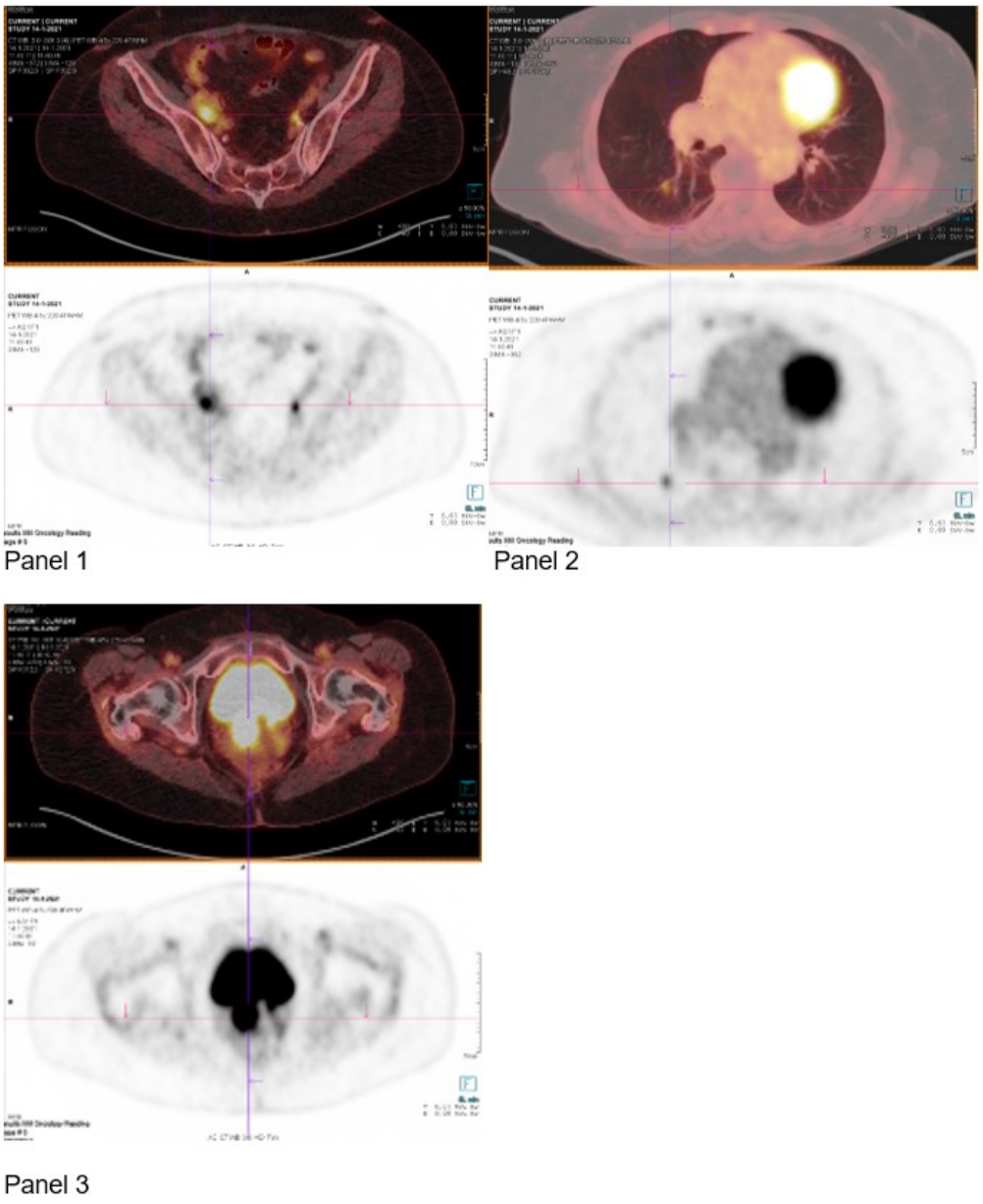


Figure 3: FDG-PET scan shows pelvic lymph nodal (Panel 1) and lung metastases (Panel 2). The tumor in the bladder is locally advanced as illustrated in panel 3.

Discussion

Primary clear cell carcinoma, also known as clear cell adenocarcinoma or mesonephroma, is a rare entity of cancer in the bladder. CCC was first described by Dow and Young in 1968 as mesonephric adenocarcinoma [14]. It is primarily a malignancy of the female genital tract. A recent thorough systematic review shows that there are currently only 70 cases of primary clear cell carcinoma in the urinary bladder described in the literature [47].

Patients usually present with hematuria or lower urinary tract symptoms, there are no other pathognomonic signs to be mentioned when CCC is involved [47]. CCC of the bladder is more common in younger age (< 60 years), black ethnicity and women [49].

The etiology of CCC in the bladder is unknown, however several hypotheses have been postulated [50,51] such as: CCC may emanate from Müllerian elements in the urinary bladder; the possibility of the involvement of the glandular tissue, such as endometriosis like genesis, in the bladder is also mentioned; CCC may represent a peculiar variant of vesical adenocarcinoma of non-Müllerian derivation and/or CCC represents a rare morphologic expression of transitional cell carcinoma, with glandular differentiation with uncertain pathway. Our patient's history of endometriosis and the immunohistochemical profile pointing at Mullerian origin

strongly suggest and support the hypothesis that CCC of the urinary bladder emerges from endometriosis and thus emanates from Müllerian derivation.

Histologically, most CCC of the bladder consists of uniform ovoid cells with a clear cytoplasm [52]. The clear cytoplasm is due to the abundant amount of glycogen in the cell, which does not stain with H&E staining, therefore the cell appears clear under the microscope, hence the name: clear cell. Glycogen has shown to have an advancing role on tumor growth, particularly during demanding circumstances such as hypoxic and nutrient deprived conditions [49]. Furthermore, glycogen has also appeared to stimulate cellular proliferation and metastasis [53].

Glycogen abundance has been suggested to preserve the Warburg effect in tumor cells. The Warburg effect is a mechanism for faster growth using glucose even under hypoxic conditions and therefore enabling the cell for survival [54]. The capability of glycogen to enhance tumor survival in critical conditions may result in faster invasion of CCCs, which could explain the higher tumor staging at diagnosis [49].

CCC has a one-year survival rate of 69.1% [47] Currently, no standard treatment has been described in literature. The majority of patients with organ confined disease receive radical cystectomy which may be curative in some cases [47]. For muscle invasive tumors, Zhou et al. suggests total rather than partial cystectomy as it leads to better survival rates [49]. Several other case reports have shown that metastatic CCC is poorly responsive to chemotherapy or radiotherapy, though further research is needed to specify this [3, 48].

Conclusion

CCC is a rare type of malignancy seldom to be found in the urinary bladder, it has both progressive and aggressive biological behaviors. Currently, radical surgery is the primary treatment choice in organ confined disease. Radiotherapy and palliative chemotherapy have shown poor clinical responses. Further research is needed to find an effective, standard treatment to increase the survival rate of this malignant disease. Increased knowledge on the advancing role of glycogen on cancer metabolism, may also lead to new treatment pathways.

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Conflicts of interest

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Not applicable

Consent to participate

Not applicable

Consent for publication

Personal details have been removed from this case description.

Availability of data and material

Not applicable

Code availability

Not applicable

Informed Consent

Informed consent is provided by the patient to publish anonymously.

Authors contribution

Z Hashemi wrote the manuscript.

H Roshani supervised and corrected the written manuscript.

KJ Lentjes reviewed and corrected the written manuscript.

D Houtsma reviewed and corrected the treatment options part of the manuscript.

R L Natté reviewed and corrected the pathological description of the specimen in the manuscript. RL Natté also contributed by sending illustrative and labeled images of the pathological

specimen.

All authors read and approved the manuscript.

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